University of Alberta

New Methods for the Preparation of Chiral α-Substituted Allylboronates and Their Synthetic Applications

by

Feng Peng ©

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Abstract

Chiral α-substituted allylboronates are very useful reagents for the enantioselective allylboration reaction, however, they are known to be difficult to prepare. Chapter 2 of this thesis describes a novel Ir-catalyzed allylic asymmetric alkylation method to synthesize these chiral α-substituted allylboronates. Synthetic applications of these new α-substituted allylboronates were demonstrated with a stereospecific allylboration reaction and an unprecedented tandem isomerization/conjugate addition reaction.

Using a different system, Chapter 3 investigates a Pd-catalyzed asymmetric alkene isomerization/allylboration reaction. This study used chiral phosphine ligands to mediate the transformation and it revealed the superiority of the Taniaphos ligand. Eventually an efficient one-pot three-component reaction was successfully developed.

Chapter 4 introduces a new family of double allylation reagents based on the concept of chiral α-substituted allylboronates. This work will challenge the perception that chiral α-substituted allylboronates can only be used to make homoallylic alcohols, since they now can also be used to access optically pure polysubstituted tetrahydrofurans, vinylcyclopropanes and oxabicyclic rings.

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Table of Contents

Chapter 1 Introduction: Allylboration Reaction Using Chiral α-Substituted Allylboronates 1

1.1 Introduction: Allylation Chemistry 1

1.2 Allylboron Reagents 2

1.3 Strategies for Enantiofacial Selective Additions of Allylboron Reagents 3

1.3.1 The use of a chiral auxiliary 3
1.3.2 The use of chiral Lewis acid and BrØnsted acid catalysis with achiral boronates 4
1.3.3 The use of chiral α-substituted allylboronates 5
1.3.3.1 [3,3] Sigmatropic rearrangement of 3-hydroxylpropenylboronates 9
1.3.3.2 Pd-catalyzed asymmetric allene diboration 10
1.3.3.3 Cu-catalyzed stereospecific allylic boration 12
1.3.3.4 Allylic tin-boron exchange 13
1.3.3.5 Methods to prepare racemic α-substituted allylboronates 14

1.4 Thesis Objectives: Development of New Catalytic, Enantioselective Methods to Prepare α-Substituted Allylboronates and their Synthetic Applications 15

1.5 References: 17

Chapter 2 Preparation of α-Substituted Allylboronates by Iridium-catalyzed Asymmetric Allylic Alkylation of 1-Propenylboronates 19

2.1 Introduction 19

2.2 Project Plan 21

2.3 Optimization of the Reaction 22

2.3.1 Preparation of 3-hydroxypropenyl boronate substrates 22
2.3.2 Results and discussion 23

2.4 Conclusions and Future Work 27

2.5 Experimental 27

2.5.1 General 27
2.5.2 Materials 28
2.5.3 Preparation of boronic ester precursor 28

2.5.3.1 Typical procedure for the preparation of boronic ester. 28
2.5.3.2 (*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl acetate 28
2.5.3.3 (*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-phenylallyl acetate 29
2.5.3.4 Methyl (*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl carbonate 29
2.5.3.5 Methyl (*E*)-3-(4,4,5,5-tetraphenyl-1,3,2-dioxaborolan-2-yl)allyl carbonate 30
2.5.3.6 Methyl (*E*)-3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)allyl carbonate ... 30
2.5.4 Preparation of α-substituted allylboronates 31
2.5.4.1 Typical procedure for iridium-catalyzed allylic asymmetric alkylation 31
2.5.4.2 Dimethyl 2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)malonate 31
2.5.4.3 Dimethyl 2-((*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)malonate 32
2.5.5 Allylboration reaction using reagents 12c 32
2.5.5.1 Dimethyl 2-((*E*)-4-hydroxy-4-phenylbut-1-enyl)malonate 32
2.5.5.2 Dimethyl 2-((*E*)-4-hydroxy-6-phenylhex-1-enyl)malonate 33
2.5.5.3 5-phenylpentane-1,3-diol 33
2.6 References: 34

Chapter 3 Palladium-Catalyzed Asymmetric Alkene Isomerization /Allylboration Reaction 36

3.1 Introduction 36
3.2 Optimizations of the Reaction and Discussions 40
3.2.1 Preparation of the starting material 40
3.2.2 Optimization process 40
3.3 Conclusions and Future Direction 46
3.4 Experimental 46
3.4.1 General 46
3.4.2 2-(3,4-dihydro-2*H*-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 47
3.4.3 1-(5,6-dihydro-2*H*-pyran-2-yl)-3-phenylpropan-1-ol 48
3.5 References: 48

Chapter 4 Development of Simple, Stable, and Versatile Double-Allylation Reagents for the Stereoselective Preparation of Skeletally Diverse Compounds 50

4.1 Introduction 50

4.2 Project Plan....52
4.3 Optimization of the Reaction....53
4.3.1 Preparation of reagents....53
4.3.2 Results and discussion....55
4.4 Conclusions and Future Directions....62
4.5 Experimental....63
4.5.1 General information....63
4.5.2 Determination of enantiomeric excess, diatereoselectivity and E/Z ration...63
4.5.3 Preparation of alkenylboronic ester precursors....64
4.5.4 Preparation of reagents 15, 17 and 19....64
4.5.5 General procedure for the allylboration reaction....66
4.5.6 (*R*,*E*)-7-(trimethylsilyl)-1-phenylhept-5-en-3-ol....66
4.5.7 (*R*,*E*)-1-(trimethylsilyl)dodec-2-en-5-ol....67
4.5.8 (*S*,*E*)-2-methyl-7-(trimethylsilyl)hept-5-en-3-ol....67
4.5.9 (*S*,*E*)-1-(benzyloxy)-6-(trimethylsilyl)hex-4-en-2-ol....68
4.5.10 (*S*,*E*)-5-(trimethylsilyl)-1-phenylpent-3-en-1-ol....68
4.5.11 (*S*,1*E*,5*E*)-7-(trimethylsilyl)-1-phenylhepta-1,5-dien-3-ol....69
4.5.12 (*S*,2*E*,6*E*)-8-(trimethylsilyl)octa-2,6-dien-4-ol....69
4.5.13 (*S*,*E*)-1-(trimethylsilyl)dodec-2-en-6-yn-5-ol....70
4.5.14 (*E*,3*R*,4*R*)-4-methyl-7-(trimethylsilyl)-1-phenylhept-5-en-3-ol....70
4.5.15 (*E*,2*S*,3*R*)-1-(benzyloxy)-3-methyl-6-(trimethylsilyl)hex-4-en-2-ol....71
4.5.16 (*E*,1*S*,2*R*)-2-methyl-5-(trimethylsilyl)-1-phenylpent-3-en-1-ol)....71
4.5.17 (*E*,3*R*,4*S*)-4-methyl-7-(trimethylsilyl)-1-phenylhept-5-en-3-ol....72
4.5.18 (*E*,2*S*,3*S*)-1-(benzyloxy)-3-methyl-6-(trimethylsilyl)hex-4-en-2-ol....72
4.5.19 (*E*,1*S*,2*S*)-2-methyl-5-(trimethylsilyl)-1-phenylpent-3-en-1-ol)....73
4.5.20 Determination of absolute stereochemistry of compound 22....74
4.5.21 General procedure for the synthesis of polysubstituted tetrahydrofurans...74
4.5.22 Tetrahydro-5-phenethyl-2-phenyl-3-vinylfuran....74
4.5.23 "One-pot" three-component reaction to form 24....75
4.5.24 2-heptyl-tetrahydro-5-phenethyl-3-vinylfuran....75
4.5.25 2-((benzyloxy)methyl)-tetrahydro-5-phenyl-3-vinylfuran....76
4.5.26 (2*S*,3*R*,5*R*)-tetrahydro-2-methyl-5-phenethyl-2-propyl-3-vinylfuran....76
4.5.27 2-((benzyloxy)methyl)-tetrahydro-4-methyl-5-phenethyl-3-vinylfuran....77
4.5.28 (2*R*,3*S*,4*R*,5*R*)-2-((benzyloxy)methyl)-tetrahydro-4-methyl-5-phenethyl-3-vinylfuran....77
4.5.29 General procedure for the synthesis of compounds 26....78
4.5.30 1-(2-((1*S*,2*R*)-2-vinylcyclopropyl)ethyl)benzene....78
4.5.31 (1*S*,2*R*)-1-heptyl-2-vinylcyclopropane....79
4.5.32 1-((((1*S*,2*R*)-2-vinylcyclopropyl)methoxy)methyl)benzene....79
4.5.33 1-(2-((1*S*,2*S*,3*R*)-2-methyl-3-vinylcyclopropyl)ethyl)benzene....80
4.5.34 General procedure for the synthesis of compounds 25....80
4.5.35 1-methyl-7-vinyl-8-oxa-bicyclo[3.2.1]octane....81
4.5.36 6-methyl-1-phenyl-7-vinyl-8-oxa-bicyclo[3.2.1]octane....81

4.6 References: 82

Appendix: X-Ray Crystallography Report of Compound 25b (Chapter 4)..... 84

List of Tables

Table 1-1 Allylboration using reagent **3** 8

Table 2-1 Synthesis of various starting material **11** 22
Table 2-2 Optimization of the reaction 24

Table 3-1 Solvent screen in the isomerization reaction 43
Table 3-2 Screening of different bases 44
Table 3-3 Effect of reaction temperature 44
Table 3-4 Effect of reaction time 45
Table 3-5 Early optimization of Taniaphos ligand 45

Table 4-1 Scope of aldehydes in addition with reagent **15** 56
Table 4-2 Modified conditions with cinnamaldehyde 57
Table 4-3 Scope of aldehydes in addition with crotylreagents **17** and **19** 58
Table 4-4 Preparation of polysubstituted tetrahydrofurans 59
Table 4-5 Preparation of vinylcyclopropanes 62

List of Figures

Figure 1-1 Two main types of allylmetal reagents **2**

Figure 1-2 Common stereoselective allylboration reagents....3

Figure 1-3 Optically pure α-substituted allylboronates....5

Figure 1-4 Transition states in the allylation of aldehydes with α-substituted allylboronates....7

Figure 1-5 Transition state for equation 1-6....12

Figure 1-6 Versatile double allylation reagent....16

Figure 2-1 Phosphoramidite ligands for Ir-catalyzed asymmetric allylic alklation....21

Figure 2-2 Catalytic allylic alkylation strategy for the regio- and enantioselective preparation of chiral α-substituted allylboronates....21

Figure 3-1 Natural products containing α-hydroxyalkyl dihydropyran or benzodihydropyran units....36

Figure 3-2 Natural products synthesized using [4+2]cycloaddition/allylboration reaction....38

Figure 3-3 Chiral phosphine ligands screen....42

Figure 4-1 Three types of double-allylation reagents....50

Figure 4-2 Diisopropyl 2-[(*E*)-γ-(dimethylphenylsilyl)]allyl-1,3,2-dioxaborolane-4,5-dicarboxylate....51

Figure 4-3 Diboron double-allylation reagents from Roush and co-workers....51

Figure 4-4 Diboron double-allylation reagent from Barrett and co-workers....51

Figure 4-5 Disilicon double allylation reagent....52

Figure 4-6 New design of double-allylation reagent....52

Figure 4-7 Allylboration reaction using reagent **15**....56

Figure 4-8 Transition state for the furan formation....60

Figure 4-9 Mechanism for the formation of oxabicycle compound....61

List of Schemes

Scheme 1-1 Preparation of reagents **1** and **2**.....6

Scheme 1-2 Preparation of reagent **3**.....6

Scheme 1-3 Pietruszka's method to prepare α-substituted allylboronates.....9

Scheme 1-4 Diastereoselective [3,3] rearrangement to prepare reagent **14** 10

Scheme 1-5 Proposed mechanism for Pd-catalyzed diboration of allens.....11

Scheme 1-6 Proposed mechanism for Cu-catalyzed allylic boration.....13

Scheme 1-7 Allylic tin-boron exchange 13

Scheme 1-8 Vinylogous Matteson rearrangement 14

Scheme 1-9 Vinylogous Matteson rearrangement 14

Scheme 1-10 Pd-catalyzed isomerization/allylboration 16

Scheme 2-1 Regioselectivity in Pd- and Ir-catalyzed alkylation of unsymmetrical substrates.....19

Scheme 2-2 Allylboration reaction using **12c**.....26

Scheme 3-1 Catalytic enantioselective [4+2]cycloaddition/allylboration reaction.....37

Scheme 3-2 Proposed mechanism for the formation of **6a**.....39

Scheme 3-3 Chiral-borane approaches.....41

LIST OF ABBREVIATIONS

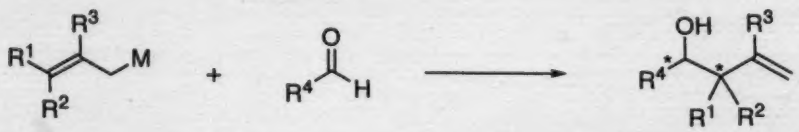
AAA	Asymmetric allylic alkylation
Al	Aluminum
B	Boron
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
BINOL	1,1'-bi-2-naphthol
Bn	Benzyl
°C	degree Celcius
Calcd.	Calculated
Cb	Diisopropylcarbamate
^{13}C NMR	carbon-13 magnetic resonance
COD	1, 5-cyclooctadiene
Cy	Cyclohexyl
dba	(1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one
DCM	Dichloromethane
DICHED	1, 2-Dicyclohexyl-1, 2-ethanediol
DME	1, 2-Dimethoxyethane
DMF	*N,N*-dimethylformamide
dr	Diastereomeric ratio
E	Entgegen
ee	Enantiomeric excess
EI	electron impact
ES	electrospray
equiv.	equivalents
Et	Ethyl
h	hour
^{1}H NMR	Proton magnetic resonance
HRMS	high resolution mass spectrometry

Ipc	Isopinocampheyl
IR	infrared spectroscopy
Ir	Iridium
J	Coupling constant
L.A.	Lewis acid
LDA	Lithium diisopropylamine
Li	Lithium
Me	methyl
MeOH	methanol
Mo	Molybdenum
OTf	fluoromethanesulfonate
Pd	Palladium
Ph	Phenyl
i-Pr	Isopropyl
Pt	Platinum
Rh	Rhodium
r.t.	room temperature
Si	Silicon
Sn	Tin
T	temperature
TADDOL	α, α, α', α'-tetraaryl-1,3-dioxolan-4,5-dimethanol
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
Ti	Titanium
TMS	Trimethylsilane
TROSY	Transverse relaxation-optimized spectroscopy
Ts	4-methylsulfonyl
W	Tungsten
Z	Zusammen
Zn	Zinc
δ	chemical shift downfield from TMS

Chapter 1 Introduction: Allylboration Reaction Using Chiral α-Substituted Allylboronates

1.1 Introduction: Allylation Chemistry

Carbonyl allylation[1] is a fundamental and very important reaction in organic chemistry. The homoallylic alcohols or propianate units generated from this reaction are found in many bioactive natural products. Today, allylation methods are used routinely in the total synthesis of polyketide natural products.[2] In particular, allyl-metals derived from B, Si, Sn, Ti and Zn have been the popular allylation reagents (Equation 1-1).



M = B, Si, Sn, Ti, Zn

Polyacetate or polypropionate units

Equation 1-1 Allylmetal additions to aldehydes

According to Denmark's interpretation,[3] these allylmetal reagents have been classified mainly into two mechanistically different types (Figure 1-1). Type I, which contains B, $SiCl_3$, Zn, etc, reacts with carbonyl compounds via a closed, chair-like, Zimmerman-Traxler transition state, in which the metal is coordinated to the carbonyl oxygen. Due to this behavior, the reaction is diastereospecific and highly diastereoselective. Generally, Lewis acid catalysts are not necessary for Type I reagents, because the substrates are activated by the allyl-metal itself. Type II reagent, which contains SiR_3, SnR_3, Mg, etc, on the other hand, reacts through an open-chain transition state. The reaction is not diastereospecific and external Lewis acid catalysts are often used to activate the carbonyl substrates.

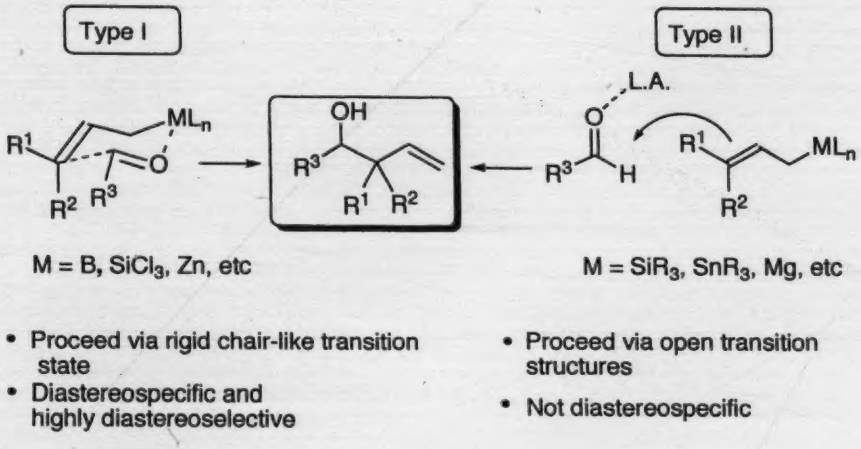


Figure 1-1 Two main types of allylmetal reagents

1.2 Allylboron Reagents

Allylboron reagents include allylic boranes and allylic boronic esters. Generally, allylic boranes are more reactive towards aldehydes than allylic boronic esters. Since the first report in 1964 by Mikhailov and Bubnov, [4] allylboron reagents have been used widely and proved to be very versatile in carbonyl allylation chemistry. Their addition to aldehydes are highly stereoselective and predictable. Boron as an element is less toxic and causes less environmental problems.

Allylic boronic esters are moisture and air stable compounds and they are more easily isolable than allylic boranes. They do not undergo the undesired allylic rearrangement[5] at room temperature. In this respect, allylic boronic esters are more suitable for bench chemists.

1.3 Strategies for Enantiofacial Selective Additions of Allylboron Reagents

Based on almost 30 years of development, the allylboration reaction is a very important tool to prepare optically pure homoallylic alcohols. Generally, there are three strategies for controlling the stereoselectivity in addition of allylic boron reagents to achiral aldehydes.

1.3.1 The use of a chiral auxiliary

To prepare chiral allylboron reagents, one of the main methods is to use a chiral auxiliary, like diol, diamine, terpene unit, as boron's two non-allylic substituents. These reagents are very useful for the enantioselective allylation of achiral aldehydes. The use of stochoimetric chiral directors, however, is not at all atom economical. The chiral auxiliary used here are easily accessible. After the allylboration reaction, the auxiliary has to be removed right away. Some of the auxiliaries (Figure 1-2) are still in use today, like Brown's pinane-based auxiliary and Roush's tartrate ester auxiliary.

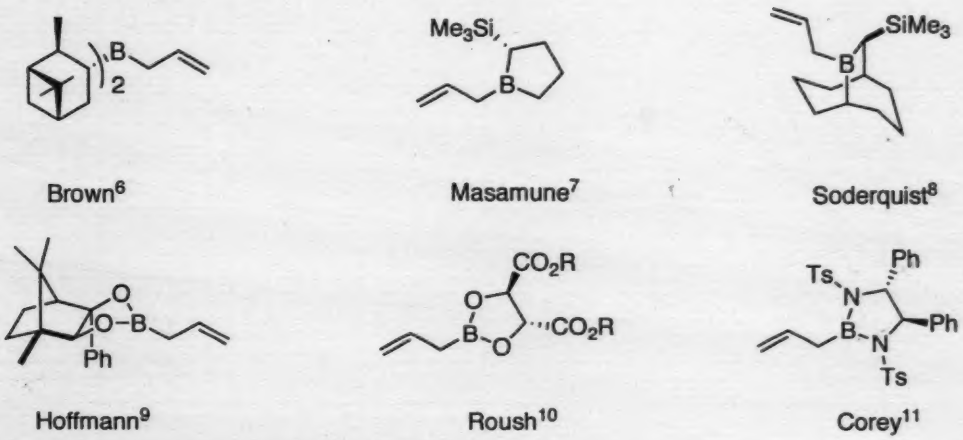
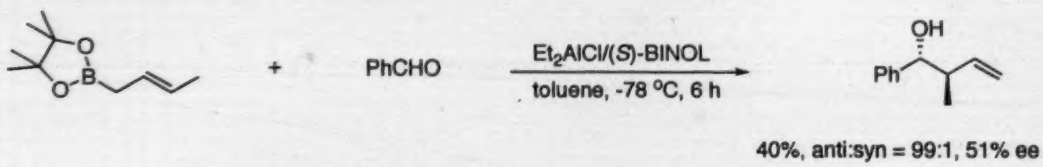


Figure 1-2 Common stereoselective allylboration reagents

1.3.2 The use of chiral Lewis acid and BrØnsted acid catalysis with achiral boronates

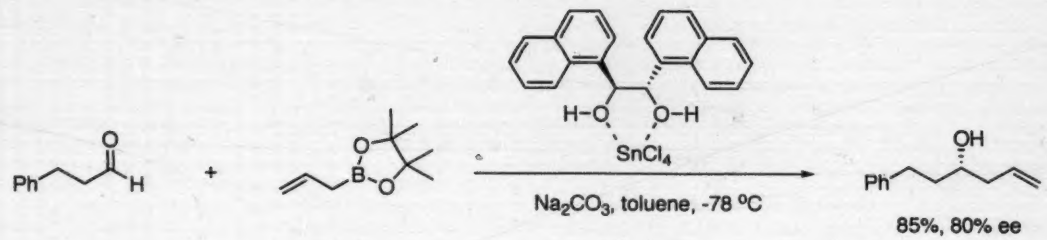
Since the discovery of Lewis acid, [12] and later, BrØnsted acid, [13] catalyzed allylboration manifolds, the possibility to develop a catalytic enantioselective allylboration reaction opened. Interestingly, the Lewis acid or BrØnsted acid catalyzed allylboration reaction remains diastereospecific.[12] Mechanistic studies[14] show that the Lewis acid or BrØnsted acid coordinates with one of the boronate oxygens and makes the boron atom more electrophilic towards the aldehydes in the cyclic Zimmerman-Traxler transition state.

The use of a chiral Lewis acid catalyst was first tested and proved to be less efficient. Results from Miyaura's group[12b] show that an allylboration reaction can be catalyzed by a chiral Lewis acid, formed from Et_2AlCl and *S*-BINOL. The homoallylic alcohol was obtained in a disappointing 51% ee (Equation 1-2).



Equation 1-2 Chiral Lewis acid-catalyzed allylboration

The use a smaller activator, a chiral proton, proved to be more efficient. Recent results from our lab[15] show that Yamamoto's chiral diol-$SnCl_4$ complexes are very efficient in this transformation. Thus, the air and moisture-stable pinacol allylboronates react with aldehydes at -78°C under the chiral diol-$SnCl_4$ complex. The homoallylic alcohol can be obtained with good yield and about 80% ee (Equation 1-3).



Equation 1-3 Chiral BrØnsted acid-catalyzed allylboration

1.3.3 The use of chiral α-substituted allylboronates.

Instead of installing the chirality on the auxiliaries, Hoffmann and co-workers prepared chiral allylboron reagents by placing the element of chirality onto the allylic units and formed optically pure **α**-substituted allylboronates, as represented by the following reagents **1**, **2**, **3**.[16, 17, 18]

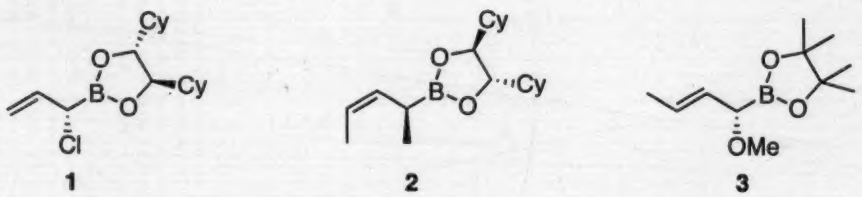
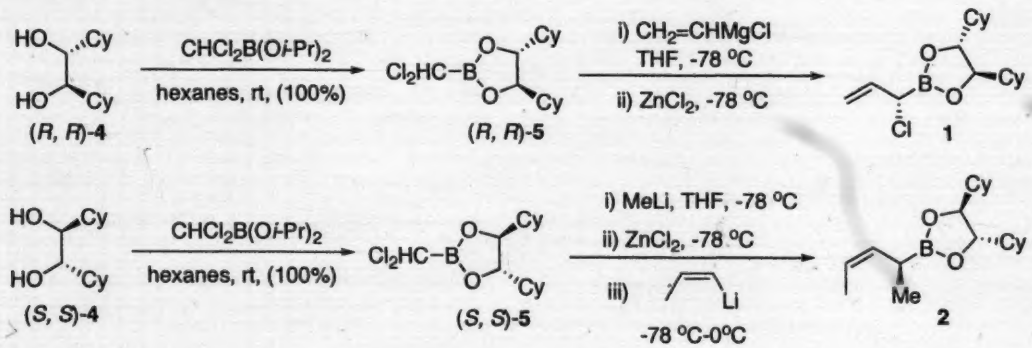


Figure 1-3 Optically pure α-substituted allylboronates

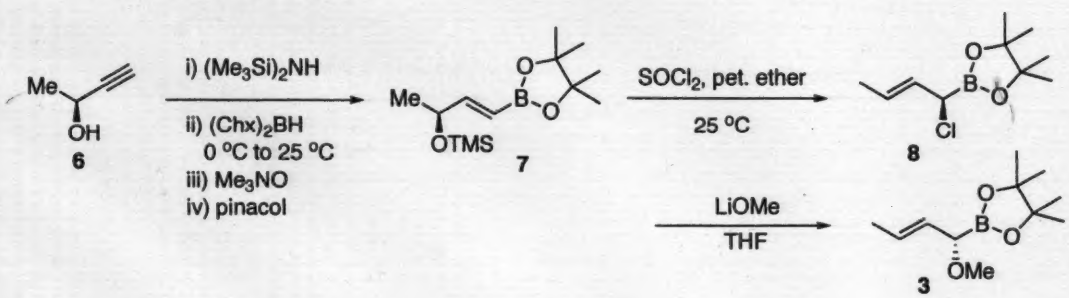
The synthesis of chiral α-substituted allyl- and (Z)-crotylboronate reagents **1**[16] and **2**[17] (Scheme 1-1) begins with commercially available (*R, R*)-DICHED. Thus, transesterification of DICHED with diisopropyl (dichloromethyl) boronate gives the chiral dichloromethylboronate **5**, a common intermediate in the synthesis of chiral alpha-substituted allylboronates by Hoffmann and co-workers. Treatment of this intermediate with vinylmagnesium chloride followed by $ZnCl_2$ leads to the (*S, R, R*)-α-chloroallylboronate, a procedure modified by Matteson.[19] This reagent is used directly in the aldehyde allylation

reaction to avoid racemization upon long-time storage.[16] Treatment of common intermediate **5** with MeLi followed by $ZnCl_2$ leads to the corresponding chiral α-chloroethylboronate **9**, which is converted to the (*S, S, S*)-(Z)-α-methylcrotylboronate via treatment with (Z)-propenyllithium using an one-pot procudure.



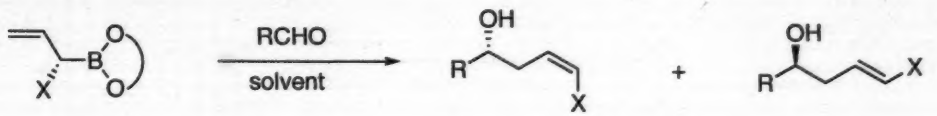
Scheme 1-1 Preparation of reagents **1** and **2**

The (*E*)-α-methoxycrotylboronate **3**[18] can be synthesized from commercially available 3-butyn-2-ol **6** (Scheme 1-2). Thus, protection of **6** as a TMS ether, hydroboration of the alkyne with dicyclohexylborane and subsequent oxidation of the borane to an alkenylboronic ester followed by transesterification with pinacol affords the intermediate **7**. Allylic rearrangement of intermediate **7** with thionyl chloride gives the chiral (*E*)-α-chlorocrotylboronate **8** in more than 98% ee. Treatment of (*E*)-α-chlorocrotylboronate **8** with LiOMe generates the (*E*)-α-methoxycrotylboronate **3**. The final step occurs with some racemization as the reagent is obtained in a reduced 90% ee.



Scheme 1-2 Preparation of reagent **3**

These chiral α-substituted allylboronates transfer their chirality completely to the newly formed stereogenic center and give two diastereomeric products when they react with achiral aldehydes. (Equation 1-4)[20]



Equation 1-4 Allylboration using optically pure α-substituted allylboronates

These two diastereoisomers are epimeric and their ratio is highly depended on the nature of the alpha substituent and the protecting group on the boron atom.[20, 21]

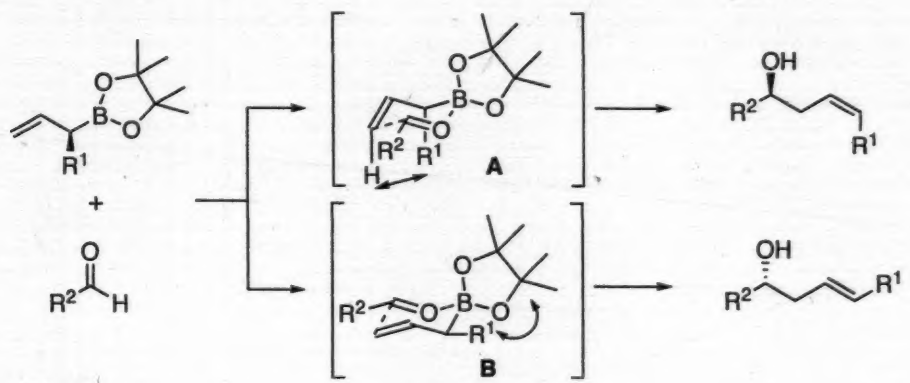
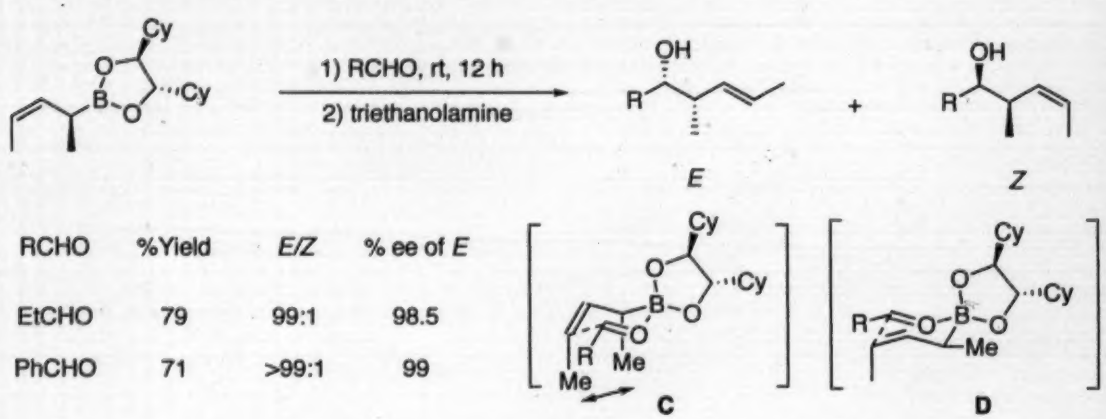


Figure 1-4 Transition states in the allylation of aldehydes with α-substituted allylboronates

The selectivity between *E* and *Z* isomers can be explained by steric and polar effects on the two competing transition states **A** and **B** (Figure 1-4). [20, 21] When the substitutes R^1 is a non-polar group like alkyl, steric effects play a dominant role. Transition state **B** can be destabilized by a steric interaction between a large boronic ester and the pseudo-equatorial alpha-substituted R^1. Transition structure **A** can minimize the interaction between R^1 and the boronic ester, however, it features unfavorable allylic interactions due to the pseudo-axial

position of the R^1 substituent. The energy difference between these two interactions is not significant, which leads to mixtures of *E* and *Z* isomer in modest selectivities. When R^1 is a polar group like –Cl, -OMe, the polar effects play an important role. In this case, transition structure **A** is favored over **B**. With the C-R^1 dipole opposite one of the B-O dipoles, it can best minimize the dipole and Coulombic repulsion.

High *E/Z* selectivity is very important for the practical use of these reagents, because it is very difficult to separate the two isomers. Generally, polar α-substituted chiral allylboronates give higher *E/Z* selectivity; non-polar α-substituted chiral allylboronates give poor *E/Z* selectivity except for the crotylboronate reagents. For example, the (*S, S, S*)-α-methylcrotylboronate **2** reacts in a highly selective manner with a variety of aldehydes to give the (*E*)-*syn* product.[22] In this reaction, the transition state **D** is favored because transition state **C** is highly destabilized by the unfavored 1, 3-pseudo-diaxial interactions between the α-methyl and the γ-methyl groups of the crotylboronate.



RCHO	%Yield	*E/Z*	% ee of *E*
EtCHO	79	99:1	98.5
PhCHO	71	>99:1	99

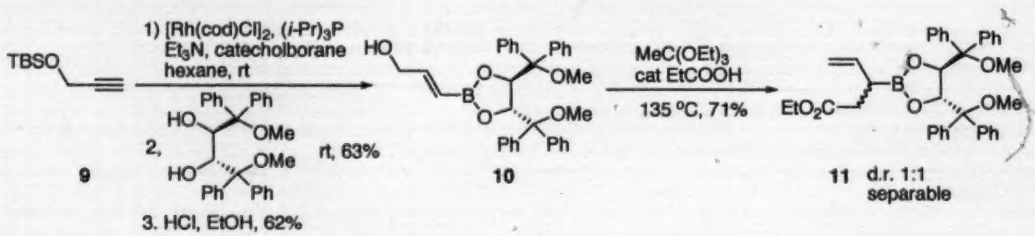
Table 1-1 Allylboration using reagent **3**

Compared with the chiral auxiliary approach, the use of chiral α-substituted allylboronates is less prevalent in the stereocontrolled-addition reaction to aldehydes. The main drawback arises from the difficulty encountered in the preparation of enantiopure reagents. The opticallly pure reagents are typically made by a Matteson asymmetric homologation of alkenylboronates, which needs expensive stoichoimetric chiral auxiliary.

Recently, several research groups reported new methods to prepare optically pure acyclic α-substituted allylboronates. These methods are summarized next.

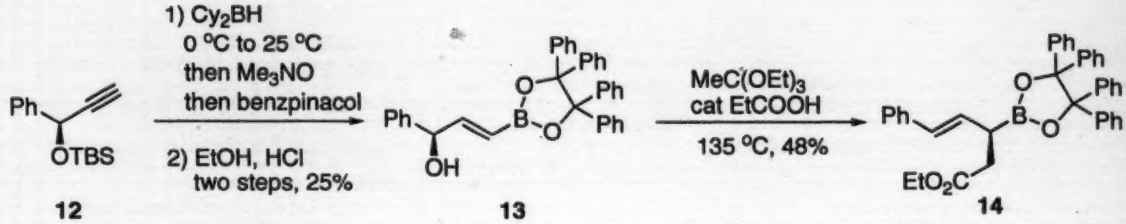
1.3.3.1 [3,3] Sigmatropic rearrangement of 3-hydroxylpropenylboronates[23]

Pietruszka and co-workers found that allylic alcohol **10** could be transformed to two seperable diastereomers under Johnson rearrangement condition (Scheme 1-3).



Scheme 1-3 Pietruszka's method to prepare α-substituted allylboronates

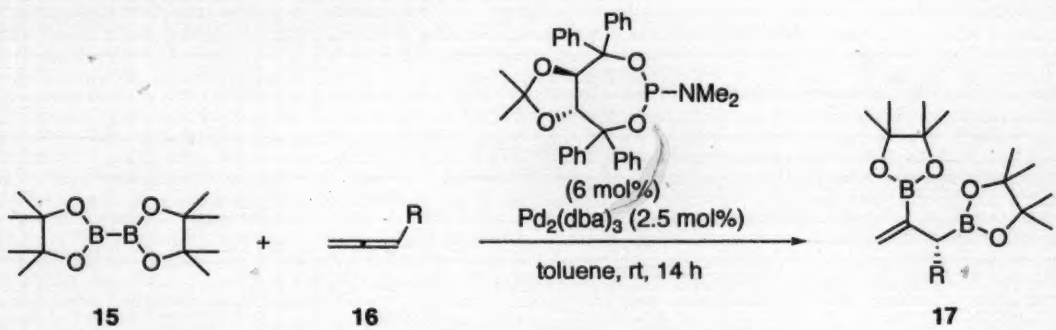
Their synthesis begins with the readily available silyl-protected propargyl alcohol **9**. Thus, hydroboration under Miyaura's catalytic conditions followed by transesterification with "inverse-TADDOL" gives intermediate **10**. Treatment of this intermediate with $MeC(OEt)_3$ and EtCOOH catalyst leads to two diastereoisomers (ratio 1:1). Purification by chromatography afforded two optically pure α-substituted allylboronates. The use of a bulky chiral auxiliary and the poor diastereoselectivity in the Johnson rearrangement make this method less attractive. Later, the same group reported a modified procedure.[24] The new method is based on a highly diastereoselective Johnson rearrangement reaction, which is showed as follows (Scheme 1-4). This method, which avoids the use of chiral auxiliary, requires enantiopure starting materials.



Scheme 1-4 Diastereoselective [3,3] rearrangement to prepare reagent **14**

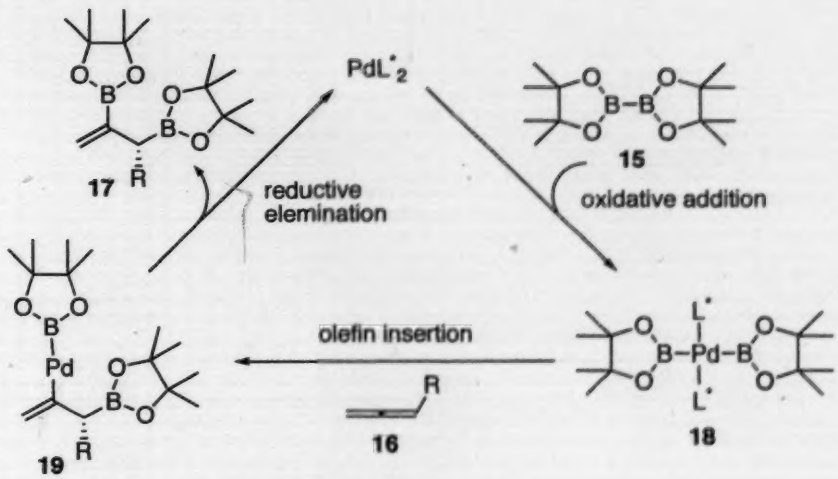
1.3.3.2 Pd-catalyzed asymmetric allene diboration[25]

In 2004, Morken and co-workers reported a catalytic, enantioselective method to prepare enantiopure α-substituted allylboronates using prochiral allenes **16** and a diboron reagent **15** as precursors (Equation 1-5).



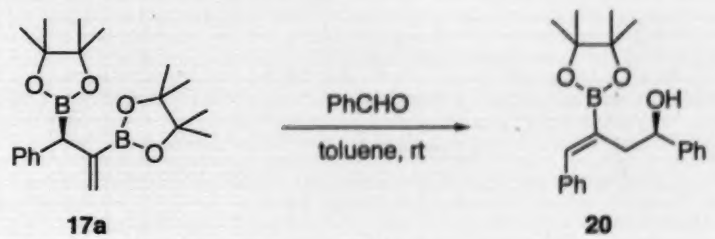
Equation 1-5 Pd-catalyzed asymmetric diboration of allenes

Excellent enantioselectivity and good yields of products **17** are obtained. The substrate scope is quite general, and mechanistically, the reaction begins with an oxidative addition of Pd(0) complex with the diboron reagent **15**, followed by insertion into the allene double bond to form intermediate **19**. Reductive elimination of **19** leads to the final product **17** (Scheme 1-5).



Scheme 1-5 Proposed mechanism for Pd-catalyzed diboration of allens

Interestingly, high diastereoselectivities are observed when these non-polar α-substituted chiral allylboronates react with achiral aldehydes (Equation 1-6). It has been proposed that the A 1, 2 interaction disfavors transition state **E**, making this pathway more energetically higher than transition state **F**.



Equation 1-6 Allylboration using diboron reagent

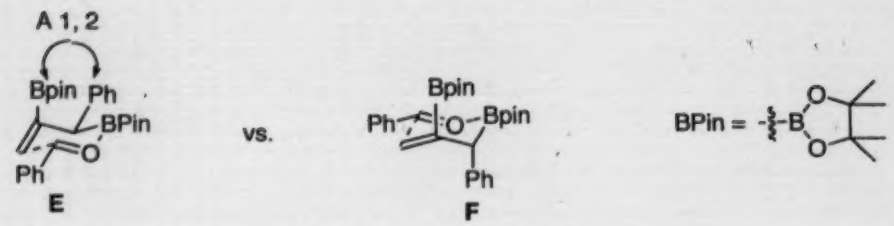
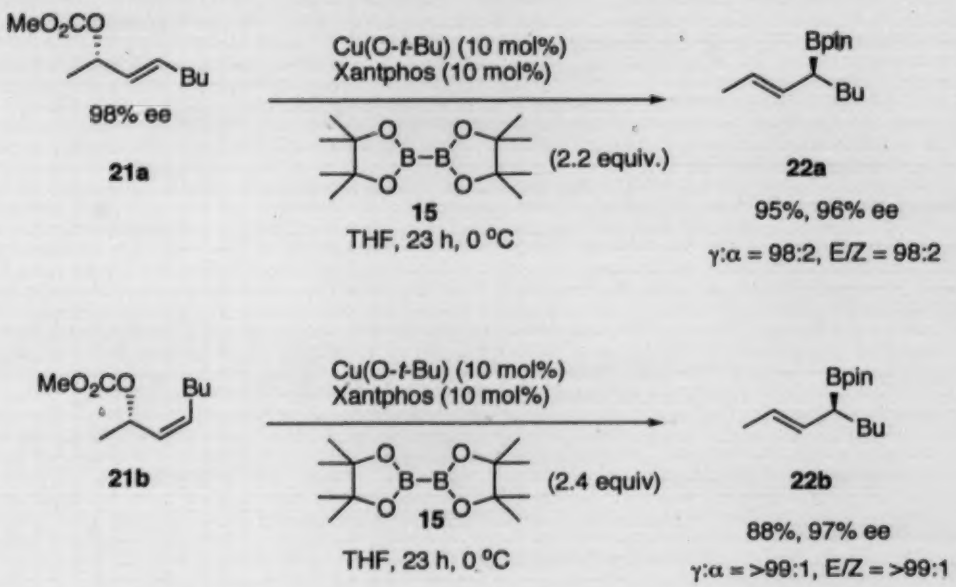


Figure 1-5 Transition state for equation 1-6

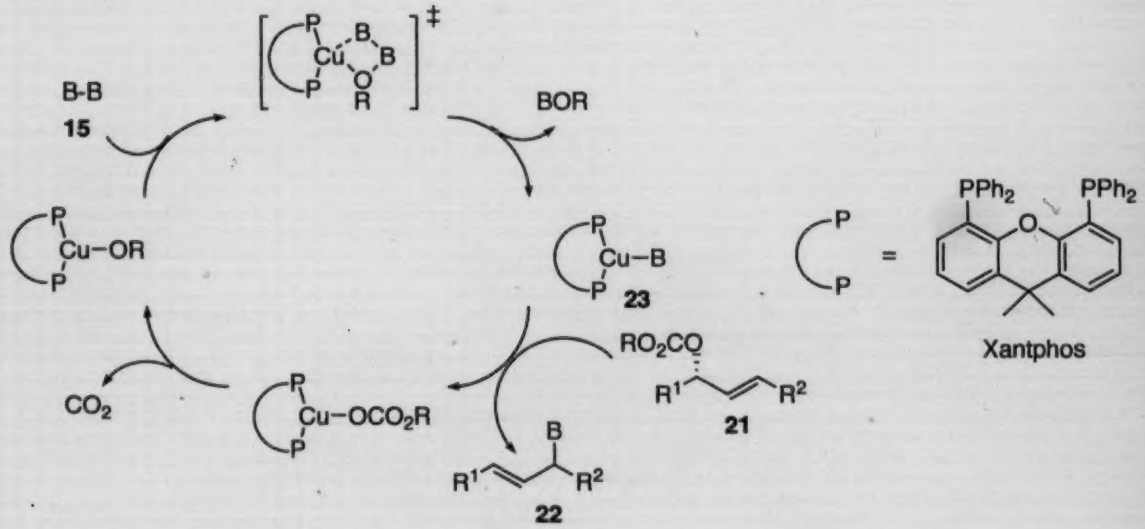
1.3.3.3 Cu-catalyzed stereospecific allylic boration[26]

Recently, Ito and co-workers reported that chiral allylboronates can be prepared using a copper-catalyzed γ-selective and stereospecific substitution reaction (Equation 1-7). This method uses chiral allylic carbonates **21** and a diboron reagent **15** as precursor. The stereoselectivity is very high and the products are obtained in excellent yields.



Equation 1-7 Cu-catalyzed stereospecific allylic boration

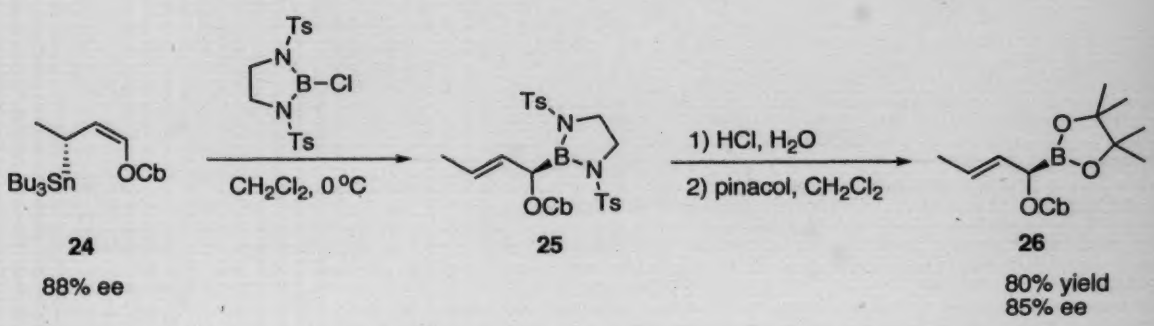
Mechanistically, the reaction begins with the σ-bond metathesis of the diboron reagent **15** with Cu(I)-OR, highly activated by Xantphos ligand. Formal S_N2' attack of the Cu-B species **23** on an allylic carbonate **21** leads to the α-substituted allylboronates **22**. The Xantphos ligand is known to have a large natural bite-angle when chelating with metals. Interestingly, the reaction also shows that the Cu-B species **23** is a "formal boryl nucleophile".



Scheme 1-6 Proposed mechanism for Cu-catalyzed allylic boration

1.3.3.4 Allylic tin-boron exchange[27]

This method has been reported by Hoppe's group. Their synthesis begins with a chiral γ-stannylated carbamate **24**. Treatment of this compound with 2-chloro-1,3-bis(toluenesulfonyl)-1,3,2-dizazborolidine in CH_2Cl_2 leads to the intermediate **25**. Hydrolysis of **25** and transesterification with pinacol gives the final crotylboronate **26** in 85% ee. The use of chiral γ-stannylated carbamate **24** as precursor, and the moderate ee of final product limit the use of this methodology.



24
88% ee

25

26
80% yield
85% ee

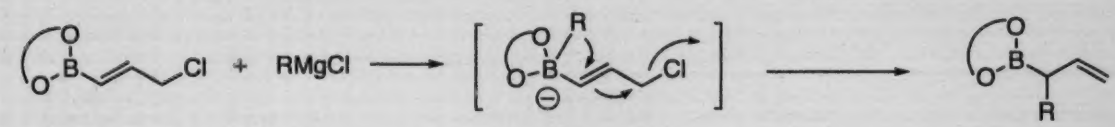
Scheme 1-7 Allylic tin-boron exchange

1.3.3.5 Methods to prepare racemic α-substituted allylboronates.

Several interesting methods to prepare racemic α-substituted allylboronates have been reported. These methods have potential to be elaborated further to gain access to optically pure α-substituted allylboronates.

Vinylogous Matteson rearrangement.

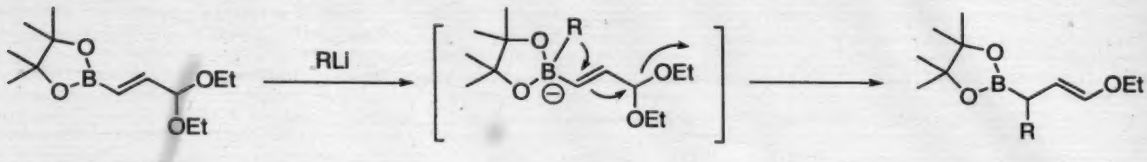
As reported by Lombardo and co-workers,[28] 'ate' complex **28a** forms when Grignard reagents react with (3-chloroprop-1-en-1-yl)boronates **27a**. These 'ate' complexes undergo anionotropic 1,3-shift to generate racemic α-substituted allylboronates **29a** (Scheme 1-8).



27a **28a** **29a**

Scheme 1-8 Vinylogous Matteson rearrangement

A similar approach has also been reported by Carreaux and co-workers.[29] In their example, 2-[(1*E*)-3,3-diethoxy-prop-1-en-1-yl]boronates **27b** have been used as substrates (Scheme 1-9). Anionotropic 1,3-shift leads to racemic α-substituted allylboronates **29b**.

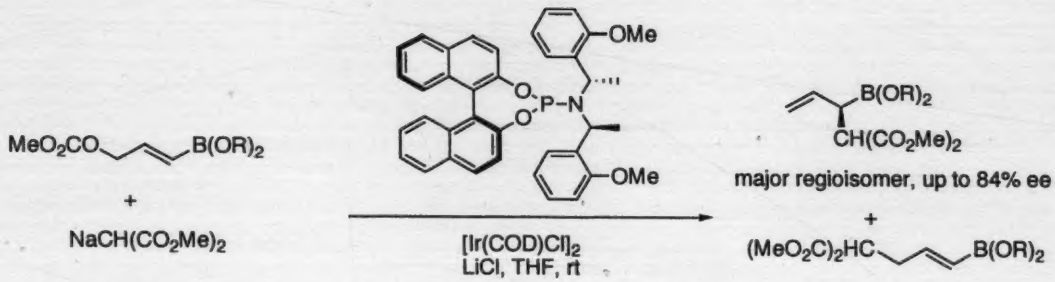


Scheme 1-9 Vinylogous Matteson rearrangement

1.4 Thesis Objectives: Development of New Catalytic, Enantioselective Methods to Prepare α-Substituted Allylboronates and Their Synthetic Applications.

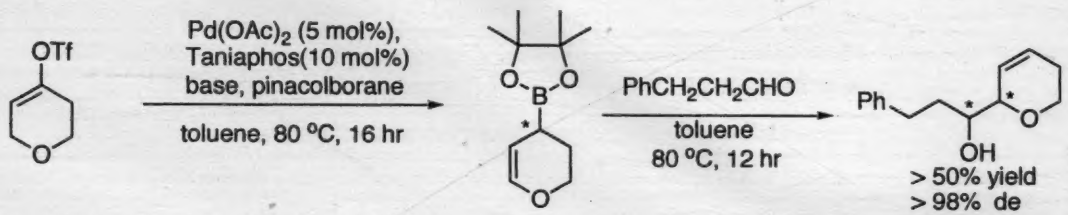
The allylboration reaction is a very useful tool to prepare optical pure homoallylic alcohols. The auxiliary-controlled approaches are well established, however, the preparation of chiral α-substituted allylboronates needs improvement. My thesis will mainly focus on the new preparations of these reagents via metal-catalyzed asymmetric transformations and their development towards synthetic applications.

Chapter 2 will describe the preparation of α-substituted allylboronates by iridium-catalyzed asymmetric allylic alkylation reactions. A brief background of asymmetric allylic alkylation reactions will be discussed in this chapter, followed by a systematic evaluation to find an iridium catalyst system and the final positive results I obtained (Equation 1-8).



Equation 1-8 Preparetion of α-substituted allylboronates by iridium-catalyzed asymmetric allylic alkylation reaction

Chapter 3 will describe the preparation of a cyclic α-substituted allylic boronate by a Pd-catalyzed asymmetric double bond isomerization. The basic challenge for this project stems from the absence of prior reports on asymmetric catalytic 1,2-alkene isomerization reaction. The optimization process of this reaction will be discussed.



Scheme 1-10 Pd-catalyzed isomerization/allylboration

Chapter 4 will describe a conceptually new family of boron-silicon double allylation reagents: α-trimethylsilylmethylallyl boronates. These stable reagents not only serve as good allylation reagents, but also can be used in the preparation of optically pure polysubstituted tetrahedrofurans, vinylcyclopropanes and larger carbocycles.

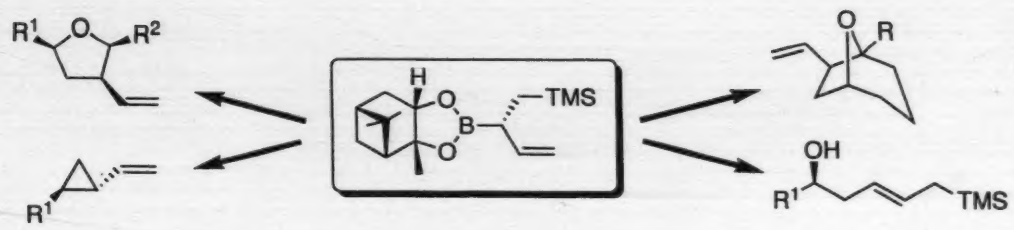


Figure 1-6 Versatile double allylation reagent

1.5 References:

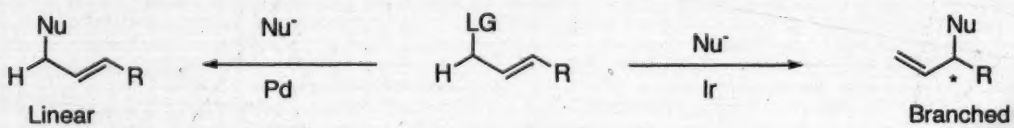
1. Denmark, S. E.; Almstead, N. D. In *Modern Carbonyl Chemistry*; Otera J., Ed,; Wiley-VCH: Weinheim, Germany, **2000**; chapter 10, pp 299-402.
2. (a) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera J., Ed,; Wiley-VCH: Weinheim, Germany, **2000**; chapter 11, pp 403-490; (b) Kennedy, J. W.; Hall, D. G. In Boronic Acids-Preparation and Applications in Organic Synthesis and Medicine; Hall, D. G.; Wiley-VCH: Weinheim, Germany, 2005; chapter 6, pp 241-277.
3. Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta*, **1983**, *66*, 1655-1660.
4. Mikhailov, B. M.; Bubnov, Y. N. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1964**, 1874-1876.
5. (a) Mikhailov, B. M.; Bogdanov, V. S.; Lagodzinskaya, G. V.; Pozdnev, V. G. *Izv. Akad. Nauk SSSR. Ser. Khim.* **1966**, 386-388. (b) Gurskii, M. E.; Gridnew, L. D.; Geiderikh, A. V.; Bubnov, Y. N.; Mstislavsky, V. L.; Ustynyuk, Y. N. *Orgnometallics*, **1992**, *11*, 4056-4061.
6. Brown, H. C.; Randad, R. S.; Bhat, K, S.; Zaidlewicz, M.; Racheria, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389-2392.
7. Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989**, *111*, 1892-1894.
8. Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044-8049.
9. Hoffmann, R. W.; Herold, T. *Chem. Ber.* **1981**, *114*, 375-383.

10. Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186-8190.
11. Corey, E. J.; Yu, C. M.; Kim, S. S.; *J. Am. Chem. Soc.* **1989**, *111*, 5495-5496.
12. (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586-11587. (b) Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414-12415. (c) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160-10161.
13. Yu, S. H.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808-12809.
14. Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518-4519.
15. Rauniyar, V.; Hall, D. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 2426-2428.
16. Sturmer, R.; Hoffmann, R. W. *Synlett.* **1990**, 759-760.
17. Hoffmann, R. W.; Ditrich, K.; Koster, G.; Sturner, R. *Chem. Ber.* **1989**, *122*, 1783-1789.
18. Hoffmann, R. W.; Dresely, S. *Chem. Ber.* **1989**, *122*, 903-909.
19. Matteson, D. S. *Acc. Chem. Res.* **1988**, *21*, 294-300.
20. Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123-130.
21. Hoffmann, R. W.; Neil, G.; Schlapbach, A. *Pure Appl. Chem.* **1990**, *62*, 1993-1998.
22. Aldersen, M.; Hildebrandt, B.; Koster, G.; Hoffmann, R. W. *Chem. Ber.* **1989**, *122*, 1777-1782.
23. Pietruszka, J.; Schone, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5638-5641.
24. Pietruszka, J.; Schone, N. *Eur. J. Org. Chem.* **2004**, 5011-5019.
25. Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 16328-16329.
26. Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034-16035.
27. Beckmann, E.; Hoppe, D. *Synthesis*, **2005**, *2*, 217-222.
28. Lombardo, M.; Morganti, S.; Tozzi, M.; Trombini, C. *Eur. J. Org. Chem.* **2002**, *16*, 2823-2830.
29. Possémé, F.; Deligny, M.; Carreaux, F.; Carboni, B. *J. Org. Chem.* **2007**, *72*, 984-989.

Chapter 2 Preparation of α-Substituted Allylboronates by Iridium-catalyzed Asymmetric Allylic Alkylation of 1-Propenylboronates

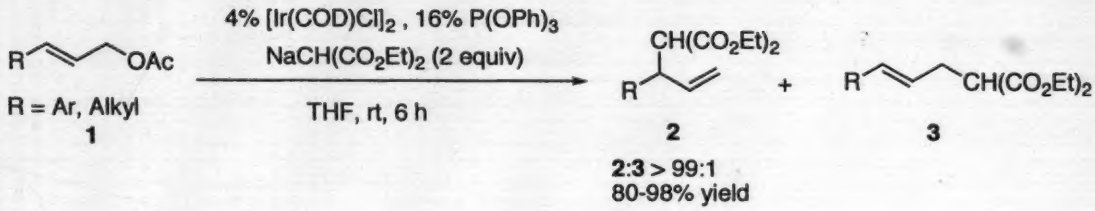
2.1 Introduction

The metal-catalyzed asymmetric allylic alkylation[1] reaction has emerged as a powerful synthetic tool. Many metals such as Pd, [2] W, [3] Rh, [4] Ir, [5] Ni, [6] Cu [7] and Pt [8] can catalyze this reaction.[2] Among these methods, the Pd-catalyzed asymmetric allylic alkylation reaction (Tsuji-Trost Alkylation) is well-established after almost 20 years of development, allowing for the highly stereoselective formation of carbon-carbon and carbon-heteroatom bonds.[2] Usually, symmetrically substituted allylic derivatives are used as substrates. When reacting with synthetically more useful unsymmetrical substrates, Pd-catalyzed allylic alkylation gives the linear product. Complementary to palladium catalyst, the newly reported Ir-catalyzed allylic alkylation leads to substitution at the more substituted carbon atom and gives optically pure branched product (Scheme 2-1).



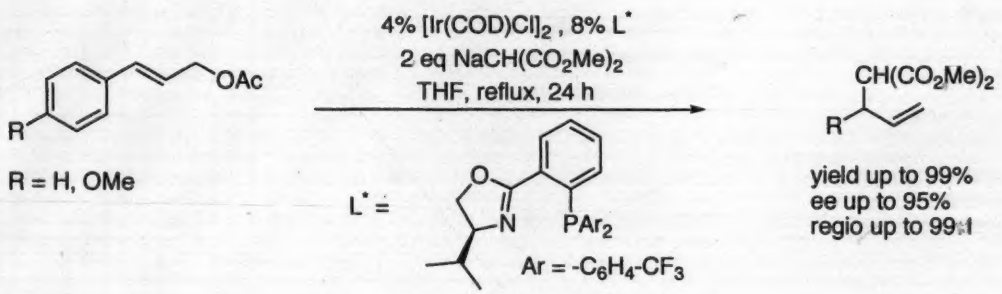
Scheme 2-1 Regioselectivity in Pd- and Ir-catalyzed alkylation of unsymmetrical substrates

The Ir-catalyzed allylic alkylation reaction was discovered in 1997.[9] Takeuchi and co-workers reported that iridium complex formed from $[Ir(COD)Cl_2]$ and $P(OPh)_3$ can efficiently catalyze allylic alkylation of unsymmetrical substrates **1** to form branched products **2** (Equation 2-1). Sodium malonate was used as the nucleophile in this reaction and the results clearly show that the regioselectivity is opposite to Pd catalysts.



Equation 2-1 Iridium-catalyzed allylic alkylation

Shortly after Takeuchi's report, an enantioselective iridium-catalyzed allylic alkylation reaction appeared.[10] In the same year, Helmchen and Janssen found that a strong π-acceptor chiral phoshinooxazoline ligand provides ee's of products up to 95% (Equation 2-2).



Equation 2-2 Asymmetric Ir-catalyzed allylic alkylation using phosphinoozazoline ligand

Several years later, Helmchen's group found that Feringa's phosphoramidite ligands **L1** and **L2** (Figure 2-1) are also very efficient in asymmetric Ir-catalyzed allylic alkylation.[11]

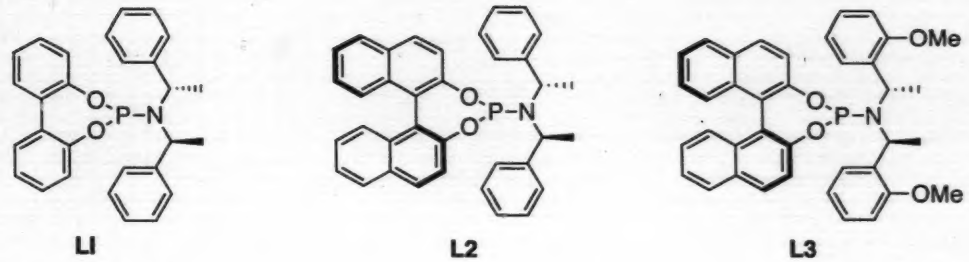


Figure 2-1 Phosphoramidite ligands for Ir-catalyzed asymmetric allylic alklation

The main drawback for these ligands is that high temperature and long reaction time are required. In 2004, a new ligand **L3** was reported and can dramatically increase the catalyst activity.[12] The reaction catalyzed by Ir and **L3** complexes can be run at room temperature and lead to products with up to 99% ee.

2.2 Project Plan

We wanted to prepare optically pure α-substituted allylboronates based on asymmetric metal-catalyzed allylic alkylation reactions (Figure 2-2). The use of achiral material in the context of catalytic method would render these α-substituted allylboronates very attractive.

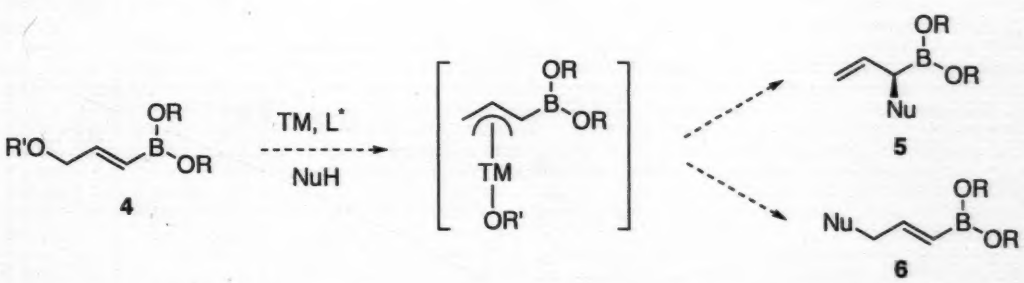
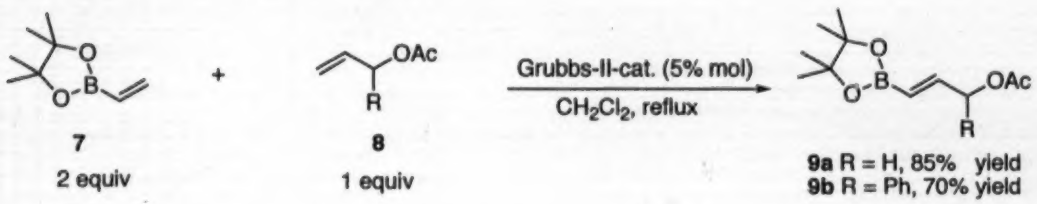


Figure 2-2 Catalytic allylic alkylation strategy for the regio- and enantioselective preparation of chiral α-substituted allylboronates

2.3 Optimization of the Reaction

2.3.1 Preparation of 3-hydroxypropenyl boronate substrates

Starting materials **9a** and **9b** were prepared using a modified Grubbs' procedure.[13] Due to the lower activity of pinacol alkenyl boronate **7** towards the *Grubbs II Catalyst* compared with the cross-coupling partner allylacetate **8**, 2 equivalents of **7** was used to reduce the amount of homo-coupling of **8** (Equation 2-3). This modified procedure leads to the desired products in good to excellent yield.



Equation 2-3 Cross-metathesis approach to prepare **9a** and **9b**

Starting material **11** were prepared using the procedure developed by our group.[14]

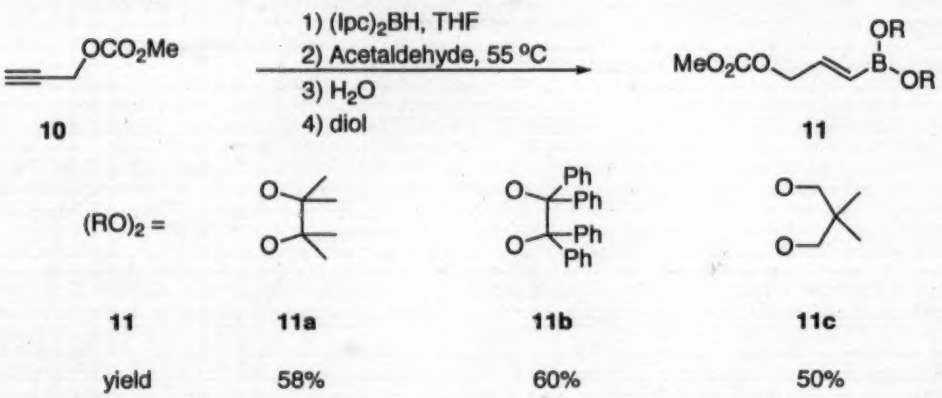


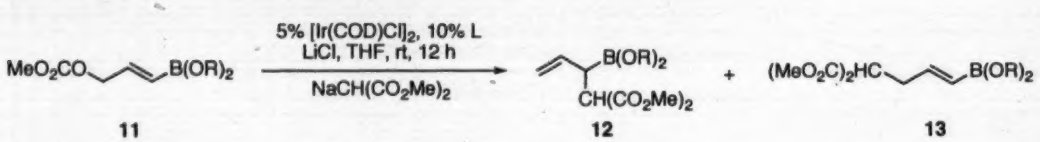
Table 2-1 Synthesis of various starting material **11**

2.3.2 Results and discussion

Our first objective was the optimization of the regioselectivity using substrates and conditions that favor the formation of the desired branched product, allylboronates **5**, over the competing alkenylboronate product **6** (Figure 2-2). This approach presents additional issues of chemoselectivity. The desired product **5** may be susceptible to further insertion into the allylic C-B bond, with consequent undesired processes such as deboronation.

Our first attempts involved the use of well-known palladium-catalyzed alkylation conditions[2] with malonate anion as mild nucleophile. Unfortunately, under all conditions investigated with various catalysts, substrates **9** led to mixtures of regioisomeric deboronation products. These compounds may originate from further undesired insertion of the metal into the desired product **5**. The use of Rh- and Mo-catalyzed alkylation led to the recovery of substrates **9**, which is probably a result of the lower catalytic activity of Rh[4] and Mo[15] toward substrate **9**.

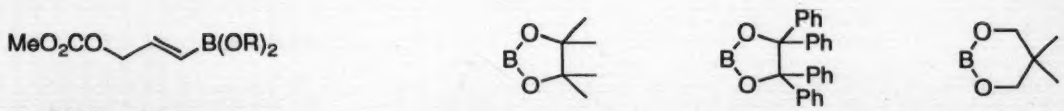
The iridium-catalyzed alkylation of the methyl carbonate derivative of 3-hydroxypropenyl boronates **11** showed more promise (Equation 2-4).

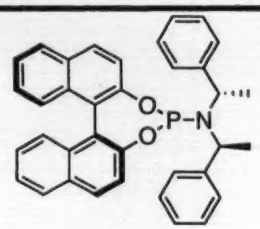


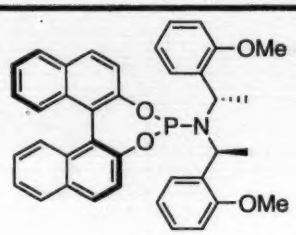
11 **12** **13**

Equation 2-4 Iridium-catalyzed alkylation of substrates **11**

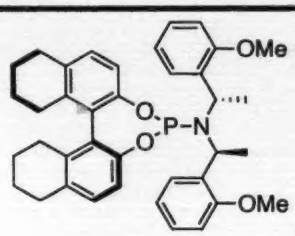
Pinacolate ester **11a** was examined first as a model substrate with dimethyl malonate as the nucleophile. As shown in Table 2-2, the regiochemistry was found to be strongly dependent on the structure of the phosphoramidite ligand.



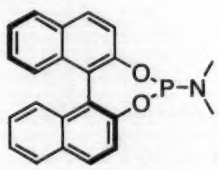

L2

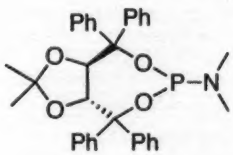


L3



L5


L6



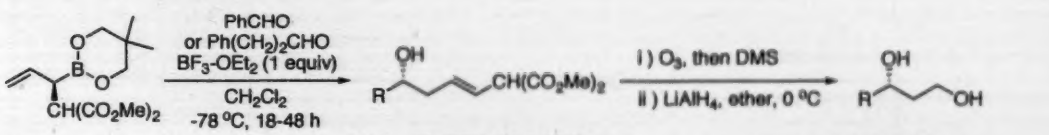
L7

Entry	Boronate	Solvent	Ligand	Ratio
1	**11a**	THF	**L6**	1:2
2	**11a**	THF	**L7**	1:6
3	**11a**	THF	**L4**	1:1.8
4	**11a**	THF	**L3**	1.7:1
5	**11a**	THF	**L4**	1:3
6	**11a**	Et_2O	**L3**	s.m.
7	**11a**	CH_2Cl_2	**L3**	s.m.
8	**11a**	Toluene	**L3**	s.m.
9	**11a**	DMF	**L3**	>1:20
10	**11a**	DMSO	**L3**	>1:20
11	**11a**	Dioxane	**L3**	1:6
12	**11b**	THF	**L3**	>1:20
13	**11c**	THF	**L3**	4.2:1
14	**11c**	THF	**L5**	1:1

Table 2-2 Optimization of the reaction

Ligand **L3** led to the largest proportion of the desired allylboronate **12a**. All other ligands favored the undesired regioisomer **13a**. Using chiral ligand **L3**, other solvents were examined. The use of ether, dichloromethane, and toluene led only to starting material probably due to the heterogeneous reaction conditions. Consequently, more polar solvents were investigated. Whereas DMF, DMSO, and dioxane led predominantly to the undesired alkenylboronate **13a**, the use of THF still provided the best ratio favoring desired regioisomer **12a**.

The effect of the boronic ester was examined next, and the size of this group was also found to have a determinant influence on the regioselectivity of the alkylation. From these results, it is clear that large boronate groups disfavor the formation of branched product **12**. Although smaller boronate **11c** led to an improved ratio favoring the desired allylboronate **12c**, it was later found that **12c** is unstable to silica gel purification. Consequently, we developed an aldehyde allylation procedure that would circumvent the need for purifying this reagent, by directly employing the crude extracted material from the alkylation reaction. As demonstrated with both benzaldehyde and hydrocinnamaldehyde, the low temperature Lewis acid-catalyzed allylboration[17] with BF_3- OEt_2 provided homoallylic alcohols **14** and **15** with excellent *E/Z* ratio[18] up to 21:1. Interestingly, the uncatalyzed reaction at room temperature afforded a reverse *E/Z* ratio of 1:4.5. Unfortunately, reagent **12c** was too sensitive to allow a direct ee measurement. However, oxidative cleavage of alkene products **14/15** and reduction of the resulting aldehyde gave diols **16** and **17** (Scheme 2-2). These two compounds were amenable to an evaluation of the optical purity, giving respectively 76% and 84% ee according to chiral HPLC analysis. A similar value can be inferred to reagent **12c** as it is well established that additions of α-substituted allylboronates occur with near-perfect stereochemical transfer.[19] The assessment of the absolute stereochemistry of **14** and **12c** was made by comparison with literature values of the optical rotation for **16**.

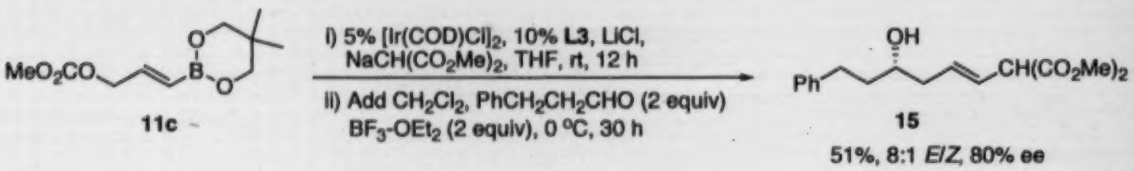


14 R = Ph (85%, 21:1 *E/Z*)
15 R = $Ph(CH_2)_2$ (70%, 16:1 *E/Z*)

16 R = Ph (85%, 76% ee)
17 R = $Ph(CH_2)_2$ (70%, 84% ee)

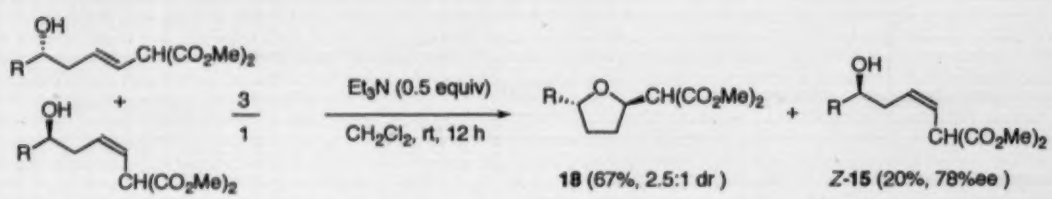
Scheme 2-2 Allylboration reaction using **12c**

Our next efforts focused on the development of a one-pot sequential allylic alkylation/allylboration. This was achieved by simply diluting the solution with CH_2Cl_2 after the allylic alkylation, and lowering the temperature to 0 °C, and add 2 equivalents each of the aldehyde and BF_3-OEt_2. We were glad to obtain the desired homoallylic alcohol in good overall yield and with an ee similar to that of the stepwise approach (Equation 2-5).



Equation 2-5 One-pot asymmetric allylic alkylation / allylboration

The allylboration products can be very useful for designing further transformation. For example, treatment of a 3:1 mixture of **15** provides a 3:1 mixture of furan **18** along with unreacted *Z*-**15**. Although the diastereoselectivity of this tandem isomerization/conjugate addition is modest, this result shows that **15** can be separated based on this *E*/*Z* selective alkoxycyclization reaction. As expected, the recovered *Z*-**15** had an optical purity of 78% ee, with an absolute configuration opposite to that of *E*-**15**.



Equation 2-6 Tandem isomerization/conjugate addition reaction

2.4 Conclusions and Future Work

In conclusion, an iridium-catalyzed asymmetric allylic alkylation approach towards the preparation of optically pure α-substituted allylboronates from simple 3-hydroxy-1-alkenylboronate precursors was developed. The allylboration reaction using these α-substituted allylboronates affords the homoallylic alcohols with ee's up to 84%. Future work in the Hall group will focus on investigating new types of ligands and new nucleophiles.

2.5 Experimental

2.5.1 General

All reactions were performed in oven-dried glassware under an argon atmosphere containing a Teflon coated stir bar and dry septum. All commercially available reagents were used without further purification. Column chromatography was performed with Ultra Pure Silica Gel (SILICYCLE, pH 6.5-7.0, 40-63 μm). TLC analyses were performed on Merck Silica Gel 60 F254 plates and were visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on Varian INOVA-300, INOVA-400, INOVA-500 MHz systems using $CDCl_3$ as solvent. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. ^1H NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; qt, quartet of triplets; dd, doublet of doublets; dt, doublet of triplets; AB, AB quartet; m, multiplet. Boron NMR spectra are referenced to external BF_3-OEt_2. High-resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) or elcrospray (ES) ionization techniques. Infrared spectra and optical rotations were recorded by University of Alberta Spectral Services and combustion analyses were performed by the University of Alberta Micro-Analytical Lab. The enantiomeric excesses for all the compounds were determined

using an HP 1100 HPLC system.

2.5.2 Materials

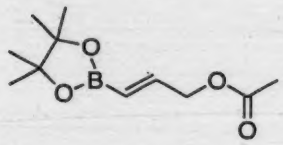
THF was freshly distilled from Na/benzophenone ketyl prior to use. Dichloromethane was freshly distilled over CaH_2 before use. Lithium chloride was dried for 24 hours at 120°C prior to use. $[IrCl(COD)]_2$ was purchased and used as received. **L2, L6** and **L7** were purchased and used as received. **L3** and **L5** were prepared according to the reported procedure.[12b]

2.5.3 Preparation of boronic ester precursor

2.5.3.1 Typical procedure for the preparation of boronic ester.[14]

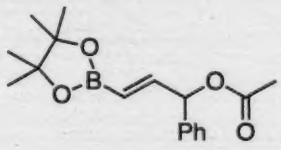
To a 50 mL flame-dried flask, add 1.0 mL of BH_3-SMe_2 (10 mmol) and 2.0 mL of dried THF under argon. To this mixture, 3.2 mL of *R*-(+)-α-pinene (20.6 mmol) was added dropwise at 0 °C. The mixture was stirred for 30 min followed by 2 h at room temperature. The resulting white suspension was cooled to -40 °C and the corresponding propargyl ester (9.8 mmol) was added slowly. The mixture was stirred for 1 h at -40 °C followed by 3 h at room temperature, then cooled down to 0 °C prior to the quick addition of 8 mL (100 mmol) freshly distilled acetaldehyde. The solution was heated to gentle reflux for 12 h and cooled back to 0 °C after which 1mL of cold water was added and the mixture was stirred for 30 min. The mixture was transferred to a separation funnel and extracted twice by ethyl acetate. The organic layers were concentrated under reduced pressure and cold hexane was added. The boronic acid precipitated and was separated by filtration. The resulting boronic acid (1 mmol) was dissolved in anhydrous THF at room temperature and the corresponding diol (1.2 mmol) was added. The mixture was stirred for 12 h and the solvent was removed under vacuo. The product was isolated by column chromatography. (hexane:ethyl acetate = 10:1)

2.5.3.2 (*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl acetate (9a)



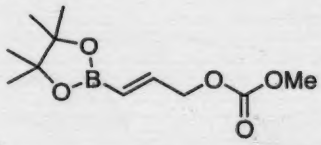
According to the procedure above, compound **9** was obtained as colorless oil (27.5 mmol, 57%) from 2-propynyl acetate (50 mmol). The product was purified by flash chromatography (hexane:ethyl acetate = 10:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.61 (ddd, J = 18.2, 4.7, 4.7 Hz, 1H), 5.68 (ddd, J = 18.1, 1.8, 1.8 Hz, 1H), 4.65 (dd, J = 4.7, 1.8 Hz, 1H), 2.09 (s, 3H), 1.27 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 145.9, 83.4, 65.4, 24.7,20.8; ^{11}B NMR ($CDCl_3$, 128 MHz) δ 29.63; IR (neat): 2980, 2934, 1745, 1648, 1381, 1232, 1145, cm^{-1}; HREIMS calcd for $C_{11}H_{19}O_4B$: 226.1376; found 226.1379 [M^+].

2.5.3.3 (*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-phenylallyl acetate (9b)



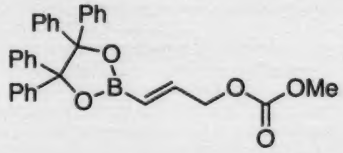
According to the procedure above, compound was obtained as colorless oil (18 mmol, 60%) from 1-phenylprop-2-ynyl acetate (30 mmol). The product was purified by flash chromatography (hexane:ethylacetate = 10:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.31 (m, 5H), 6.68 (dd, J = 18.0, 4.8 Hz, 1H), 6.60 (dd, J = 4.9, 1.7 Hz, 1H), 5.65(dd, J = 18.0, 1.7 Hz, 1H), 2.11 (s, 3H), 1.26 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 149.3, 138.3, 128.5, 128.2, 127.3, 83.5, 25.0, 24.9, 21.3;^{11}B NMR ($CDCl_3$, 128 MHz) δ 29.55; IR (neat): 2979, 2932, 1742, 1642, 1362, 1232cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{17}H_{23}O_4B$: 302.1690; found 302.1693 [M^+].

2.5.3.4 Methyl (*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl carbonate (11a)



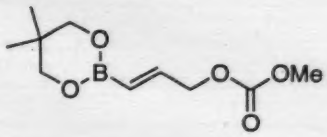
According to the procedure above, compound was obtained as colorless oil (35 mmol, 58%) from methyl prop-2-ynyl carbonate (60 mmol). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.59 (ddd, J = 18.1, 4.8, 4.8 Hz, 1H), 5.70 (ddd, J = 18.2, 1.8, 1.8 Hz, 1H), 4.70 (dd, J = 4.8, 1.8 Hz, 2H), 3.78 (s, 3H), 1.23 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.6, 145.2, 83.5, 68.8, 54.9, 24.8; ^{11}B NMR ($CDCl_3$, 128 MHz) δ 29.56; IR (neat): 2980, 2936, 1754, 1649, 1446, 1402, 1381 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{11}H_{29}O_5B$: 242.1326; found 242.1326 [M^+].

2.5.3.5 Methyl (*E*)-3-(4,4,5,5-tetraphenyl-1,3,2-dioxaborolan-2-yl)allyl carbonate (11b)



Benzopinacole (2.74 g, 7.5 mmol) and boronic acid (800 mg, 5 mmol), which was prepared according to the above procedure, were added to a 50 mL round-bottom flask containing a magnetic stir bar and 30 mL of toluene under argon. The flask was fitted with a Dean-Stark condenser and the reaction was heated at 105 °C for 24 h. The solvent was removed under reduced pressure and crude residue was purified by flash chromatography (hexane:ethylacetate = 20:1) affording a white solid (1.46g, 60%). m.p. 161-164 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.20-7.07 (m, 20H), 7.06-6.99 (m, 1H), 6.13 (ddd, J = 18.2, 1.2, 1.2 Hz, 1H), 4.88 (dd, J = 4.5, 1.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.6, 147.3, 142.4, 128.6, 128.5, 127.2, 127.0, 96.1, 68.8, 55.0; IR (solid miroscope): 3034, 2956, 1752, 1648, 1492, 1440, 1401 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{31}H_{27}O_5B$: 490.1952; found 490.1947 [M^+]. Anal. Calcd for $C_{31}H_{27}O_5B$: C, 75.93; H, 5.55. Found: C, 75.61; H, 5.59.

2.5.3.6 Methyl (*E*)-3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)allyl carbonate (11c)



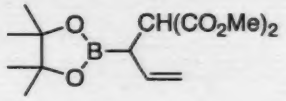
According to the procedure above, compound was obtained as colorless oil (30 mmol, 50%) from methyl prop-2-ynyl carbonate (60 mmol). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.52 (ddd, J = 17.9, 4.9, 4.9 Hz, 1H), 5.62 (ddd, J = 17.9, 1.7, 1.7 Hz, 1H), 4.69 (dd, J = 5.0, 1.7 Hz, 2H), 3.78 (s, 4H), 3.77 (s, 3H), 0.96 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.6, 142.6, 72.1, 69.1, 54.8, 31.8, 21.9; ^{11}B NMR ($CDCl_3$, 128 MHz) δ 25.73; IR (neat): 2961, 2889, 1753, 1648, 1478, 1380, 1321 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{10}H_{17}O_5B$: 228.1169; found 228.1168 [M^+].

2.5.4 Preparation of α-substituted allylboronates

2.5.4.1 Typical procedure for iridium-catalyzed allylic asymmetric alkylation

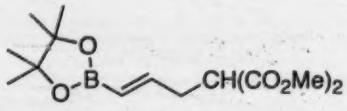
In a 5 ml flame-dried round-bottom flask, $[IrCl(COD)]_2$ (16.9 mg, 0.025 mmol), chiral ligand (0.05 mmol) and lithium chloride (42.5 mg, 1 mmol) were dissolved in 1 mL of THF under argon. The mixture was stirred for 30 min at room temperature. Boronic ester (1 mmol) was added and 5 min later, a solution of freshly prepared sodium malonate (2 mmol) in THF (2 mL) was added. The reaction mixture was stirred for 15 h at room temperature, then quenched by saturated NH_4Cl solution, extracted with diethyl ether and dried over magnesium sulfate. The product was purified by flash-column chromatography. (hexane:ethyl acetate = 15:1)

2.5.4.2 Dimethyl 2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)malonate (12a)



According to the procedure above, was obtained as yellow oil. (142 mg, 47%) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.75 (ddd, J = 17.1, 10.2, 9.1 Hz, 1H), 5.08 (d, J = 17.1 Hz, 1H), 5.01 (d, J = 10.2 Hz, 1H), 3.71-3.68 (m, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 2.50 (dd, J = 9.9, 9.9 Hz, 1H), 1.23 (s, 6H), 1.20 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.7, 169.6, 134.5, 116.7, 83.7, 53.1, 52.6, 52.3, 24.7, 24.6; ^{11}B NMR ($CDCl_3$, 128 MHz) δ 31.89; IR (neat): 2979, 2955, 1738, 1634, 1436, 1366, 1330 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{14}H_{23}O_6B$: 298.1588; found 298.1586 [M$^+$].

2.5.4.3 Dimethyl 2-((*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)malonate (13a)



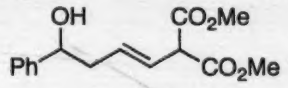
According to the procedure above, was obtained as yellow oil (90 mg, 30%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.52 (ddd, J = 17.9, 6.4, 6.4 Hz, 1H), 5.08 (dd, J = 17.9, 1.5 Hz, 1H), 5.01 (d, J = 10.2 Hz, 1H), 3.78 (m, 1H), 3.70 (s, 6H), 3.51 (t, J = 7.5 Hz, 1H), 2.77-2.73 (m, 2H), 1.23 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.2, 148.6, 121.6, 83.3, 52.6, 50.7, 34.6, 24.8; ^{11}B NMR ($CDCl_3$, 128 MHz) δ 29.53; IR (neat): 2978, 2956, 1739, 1641, 1437, 1391, 1365 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{14}H_{23}O_6B$: 298.1588; found 298.1588 [M$^+$].

2.5.5 Allylboration reaction using reagents 12c

Dimethyl 2-(1-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)allyl)malonate (**12c**) was prepared according to the typical procedure for Iridium-Catalyzed allylic asymmetric alkylation reaction. The product was not purified and used as crude. At -78 °C, 30 μL of fresh distilled benzylaldehyde (0.28 mmol, limiting reagent) was added to a 5 mL of round-bottom flask containing 1 mL of anhydrous CH_2Cl_2 and a magnetic stir bar. 24 μL of BF_3-OEt_2 was added to the aldehyde solution and 110 mg of crude **12c** was added shortly after the addition of BF3-OEt_2. The reaction was stirred at -78 °C for 20 h and then quenched with saturated $NaHCO_3$, extracted with ether. The crude ^{1}H NMR shows the E/Z ratio 21:1. The pure

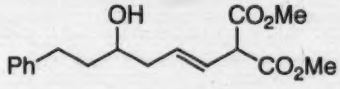
product was obtained as colorless oil (66 mg, 85%) by flash chromatography. (hexane/ethyl acetate = 4:1).

2.5.5.1 Dimethyl 2-((*E*)-4-hydroxy-4-phenylbut-1-enyl)malonate (14)



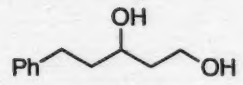
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.25 (m, 5H) 5.80 (dd, J = 15.5, 8.3 Hz, 1H), 5.68 (ddd, J = 15.6, 6.4, 6.4 Hz, 1H), 4.74 (t, J = 6.5 Hz, 1H), 4.03 (d, J = 8.3 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 2.54 (t, J = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.5, 168.5, 143.7, 132.6, 128.6, 127.6, 125.8, 125.0, 73.3, 55.3, 52.8, 42.3; IR (neat): 3029, 2954, 1735, 1653, 1636, 1495, 1436 cm^{-1}; HRMS (ESP) calcd for $C_{15}H_{18}O_5Na$: 301.1047; found 301.1047.

2.5.5.2 Dimethyl 2-((*E*)-4-hydroxy-6-phenylhex-1-enyl)malonate (15)



The procedure is similar to compound **15** and the pure product was obtained as colorless oil (54 mg, 85%) by flash chromatography. (hexane/ethyl acetate = 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.18 (m, 5H) 5.80 (dd, J = 15.5, 8.3 Hz, 1H), 5.70 (ddd, J = 15.6, 6.4, 6.4 Hz, 1H), 4.03 (d, J = 8.3 Hz, 1H), 3.78 (s, 6H), 3.65(m, 1H), 2.83-2.63 (m, 2H), 2.20-2.08 (m, 2H), 1.81-1.75(m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.8, 142.2, 133.0, 128.7, 128.6, 126.1, 125.1, 70.1, 55.5, 53.0, 52.9, 40.8, 38.7, 32.2; IR (neat): 3537, 2955, 1738, 1640, 1436, 1260 cm^{-1}; HRMS (ESP) calcd for $C_{17}H_{22}O_5Na$: 329.1359; found 329.1360.

2.5.5.3 5-phenylpentane-1,3-diol (17)



55 mg of **15** was dissolved in CH_2Cl_2 and Ozone was then bubbled through the solution at -78 °C for 1 h. Oxygen was kept passing for another 10 min to remove the excess ozone. After adding 1 mL of Me_2S, the mixture was warmed up to room temperature and the volatiles were removed under reduced pressure. The residue was dissolved in 3 mL of anhydrous ether and 100 mg of $LiAlH_4$ was added to the solution slowly. The reaction mixture was stirred at room temperature for 1 h, diluted with 3 mL of ether and treated successively with 150 μL of water, 400 μL of 2 N NaOH solution. After filtration, the solution was dried over anhydrous Na_2SO_4. The pure product was obtained as colorless oil (20 mg, 67%) by flash chromatography (hexane:ethyl acetate = 1:1). The ee was determined on a Daicel Chiralpak OD HPLC column with hexane: 2-propanol = 95 : 5, flow = 1.5 mL/min. Retention times: 23.1 min, 27.6 min; 84.4% ee; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.25 (m, 5H), 3.95-3.80 (m, 3H), 2.82-2.68 (m, 2H), 1.90-1.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.9, 128.5, 128.4, 126.0, 71.7, 62.0, 39.4, 38.5, 32.0; IR (neat): 3347, 2929, 2858, 1603, 1454 cm^{-1}; HRMS (EI, *m/z*) calcd for $C_{11}H_{16}O_2$: 180.1150; found 180.1148 [M^+].

2.6 References:

1. (a) Trost, B. M.; Lee, C. in *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: Ojima, I.), Wiley-VCH, New York, **2000**, pp. 593-649. (b) Pfaltz, A.; Lautens, M. in *Comprehensive Asymmetric Catalyst* (Ed.: Jocobsen, E. N.; Pfaltz, A.; Yamamoto, H.), Springer, Heidelberg, **1999**, pp. 833-886.
2. (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921-2944.
3. Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1995**, *34*, 462-464.
4. Hayashi, T.; Okada, A.; Suzuki, T.; Kawatsura, M. *Org. Lett.* **2003**, *5*, 1713-1715.
5. Takeuchi, R. *Synlett. 2002*, 1954-1965.
6. Bricout, H.; Carpentier, J-F.; Mortreux, A. *Tetrahedron Letts.* **1996**, *37*, 6105-6108.

7. Van Klaveren, M.; Persson, E. S. M.; del Villar, A.; Grove, D. M.; Backvall, J. E.; van Koten, G. *Tetrahedron Letts.* **1995**, *36*, 3059-3062.
8. Brown, J. M.; Machintyre, J. E. *J. Chem. Soc., Perkin Trans. 2* **1985**, 961-970.
9. Takeuchi, R.; Kashio, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 263-265.
10. Janssen, J. P.; Helmchen, G. *Tetrahedron Letts.* **1997**, *38*, 8025-8026.
11. (a) Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741-742. (b) Bartels, B.; Garcia-Yebra, C.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, 1097-1103.
12. (a) Alexakis, A.; Polet, D. *Org. Lett.* **2004**, *6*, 3529-3532. (b) Polet, D.; Alexakis, A. *Org. Lett.* **2005**, *7*, 1621-1624.
13. Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031-6034.
14. Gravel, M.; Toure, B. B.; Hall, D. G. *Org. Prep. Proc. Intl.* **2004**, *36*, 573-579.
15. Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159-167.
16. Fringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346-353.
17. (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11585-11587. (b) Rauniya, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518-4519. (c) Carosi, L.; Lachance, H.; Hall, D. G. *Tetrahedron Lett.* **2005**, *46*, 8981-8985.
18. Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 3070-3071.
19. (a) Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123. (b) Hoffmann, R. W.; Neil, G.; Schlapbach, A. *Pure Appl. Chem.* **1990**, *62*, 1993-1998.

Chapter 3 Palladium-Catalyzed Asymmetric Alkene Isomerization /Allylboration Reaction

3.1 Introduction

The α-hydroxyalkyl dihydropyran and benzodihydropyran units are found in many higher-order sugars and marine natural products (Figure 3-1). Many of these natural products display very interesting bioactivities. For examples, 2-deoxy-β-KDO is a key component of the lipopolysaccharide cell wall of Gram-negative bacteria.[1] Nebivol is found to be an anti-hypertensive agent.[2]

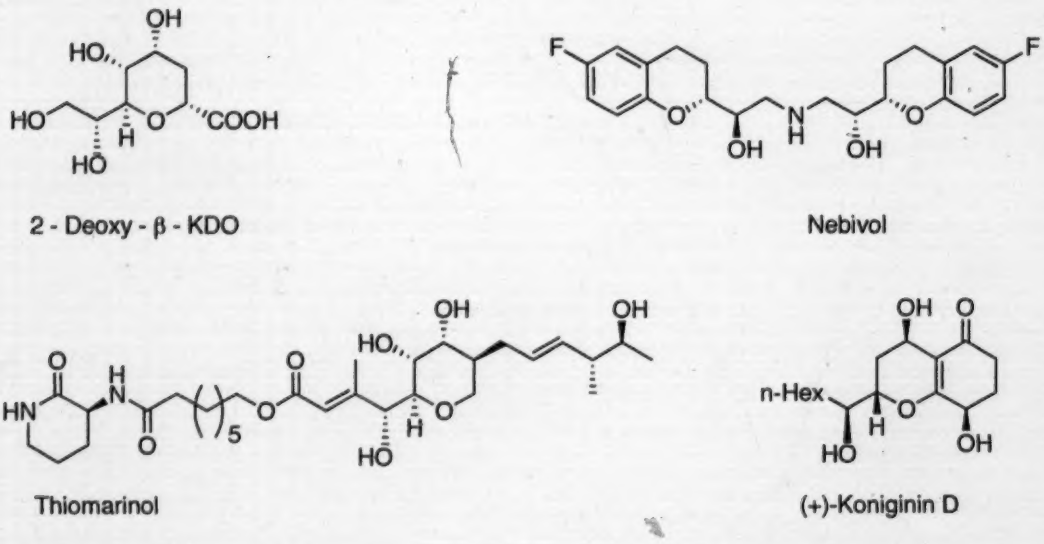
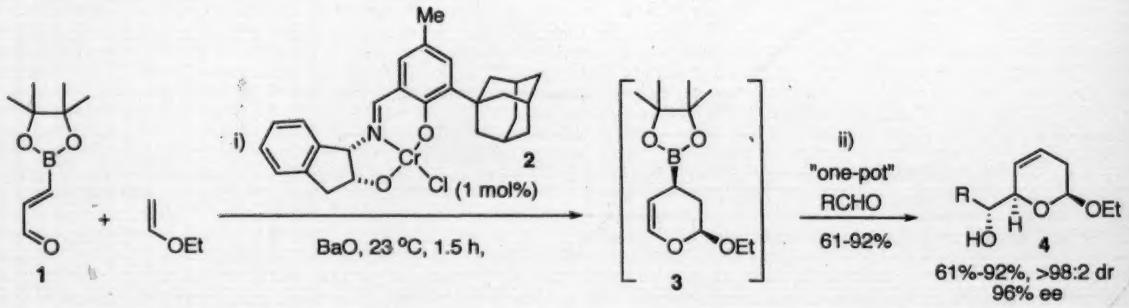


Figure 3-1 Natural products containing α-hydroxyalkyl dihydropyran or benzodihydropyran units

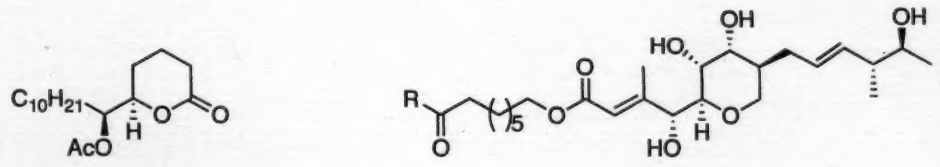
To date, few approaches have been successful to synthesize these motifs with good stereocontrol.[3] In 2003, our group developed a catalytic enantioselective hetero[4+2] cycloaddition/allylboration sequence that leads an efficient access to α-hydroxyalkyl dihydropyrans (Scheme 3-1).[4] In this work, 3-boronoacrolein pinacolate **1** was found to be a

very versatile hetereodiene in a reverse electron demand hetero[4+2] reaction with enol ethers, catalyzed by Jacobsen's chiral chromium complex **2**.[5] Without purification, product **3** reacts in a one-pot procedure with a broad scope of aldehydes and affords the α-hydroxyalkyl dihydropyrans in good to excellent yields. In addition, excellent diastereoselectivity and enantioselectivity were achieved (Scheme 3-1). The second step is highly stereoselective because compound **3** is an α-substituted allylboronate and can transfer the chirality to the product completely.[6]



Scheme 3-1 Catalytic enantioselective [4+2]cycloaddition/allylboration reaction

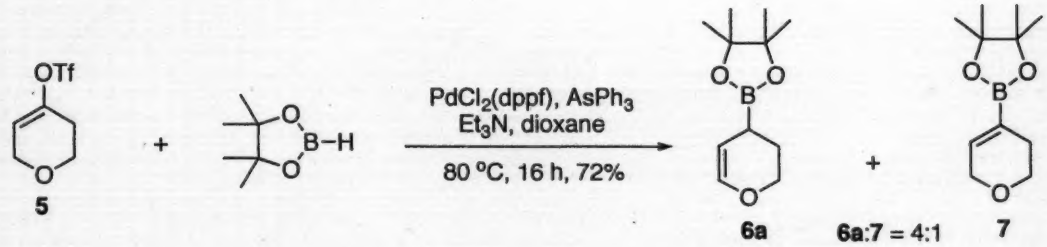
This method was successfully employed to synthesize the natural products, (5*R*, 6*S*)-6-acetoxy-5-hexadecanolide[4] and thiomarinol [7] (Figure 3-2). Remarkably, the three-component [4+2]cycloaddition/allylboration reaction significantly increases the efficiency of the synthesis of thiomarinol (22% yield from **1**). The main limitation of this methodology is the requirement for a further reduction of the ethyl acetal group, which was introduced in the cycloaddition step. This selective reduction requires several steps of protecting group manipulations. Therefore, a simpler derivative of compound **3**, which does not contain the ethyl acetal group, would potentially be more synthetically useful in a general sense.



(5*R*, 6*S*)-6-acetoxy-5-hexadecanolide thiomarinols

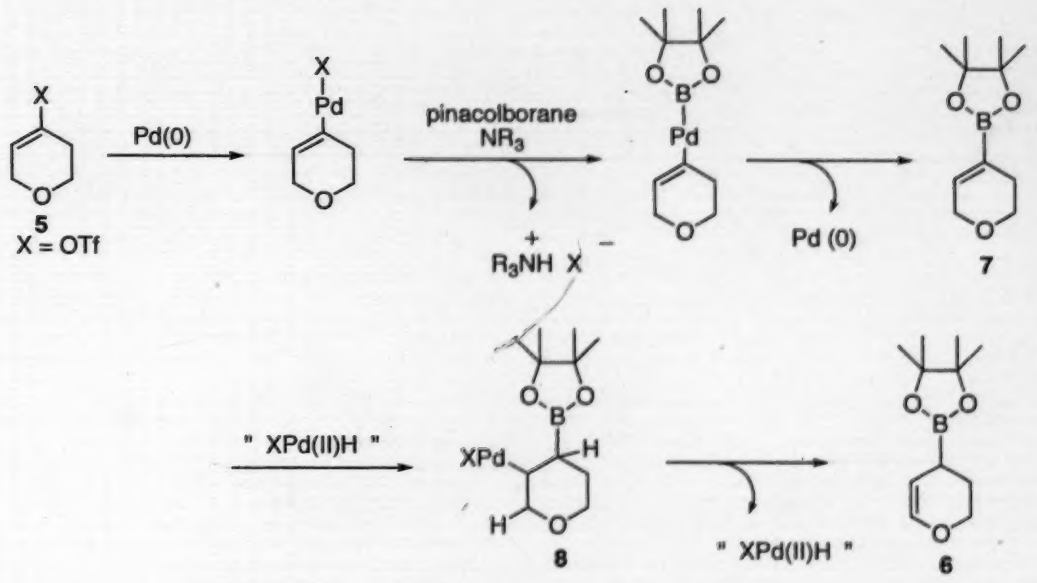
Figure 3-2 Natural products synthesized using [4+2]cycloaddition/allylboration reaction

In 2000, Masuda and co-workers reported a palladium-catalyzed borylation of alkenyl triflates using pinacolborane.[8] Interestingly, alkenyl triflate **5** affords predominantly isomerization product **6a** (Equation 3-1).



Equation 3-1 Palladium-catalyzed borylation of alkenyl triflate **5**

This reaction gained our attention because Masuda's undesired product **6a** is exactly what we wanted. Mechanistically, we propose that the reaction begins with an oxidative addition of Pd(0) catalyst with **5**, followed by transmetallation and reductive elimination to afford product **7**. Then, addition of H-Pd-X to compound **7** leads to intermediate **8**. The later β-hydride elimination generates the final product **6a** (Scheme 3-2).



Scheme 3-2 Proposed mechanism for the formation of **6a**

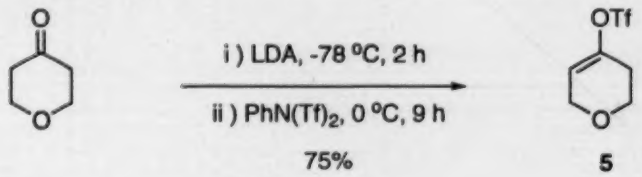
Based on the proposed mechanism, we examined the possibility of elaborating this reaction to its more attractive enantioselective version. We rationale that a stereoselective insertion of H-Pd-X species to compound **7** can generate the optically pure intermediate **8** and the following β-elimination will afford the optically pure product **6a**. Thus, this project was initiated. Our goal was to find a mild condition, which can selectively generate product **6a** in high enantioselectivity.

Fundamentally, the challenge we faced here is to develop a palladium-catalyzed, enantioselective, 1,2-alkene isomerization reaction using allylic ether substrates. To date, other metals, like the cationic Iridium complex, are reported as efficient catalysts for 1,2-alkene isomerization reaction, however, there is no report about an enantioselective 1,2-alkene isomerization of allylic ether variant yet.[9a, 9b, 9c] Chiral diphosphine Rhodium(I) complexes were also reported for enantioselective isomerization of prochiral allylamines, but these systems did not work well for the allylic ethers.[9d,9e]

3.2 Optimization of the Reaction and Discussions

3.2.1 Preparation of the starting material

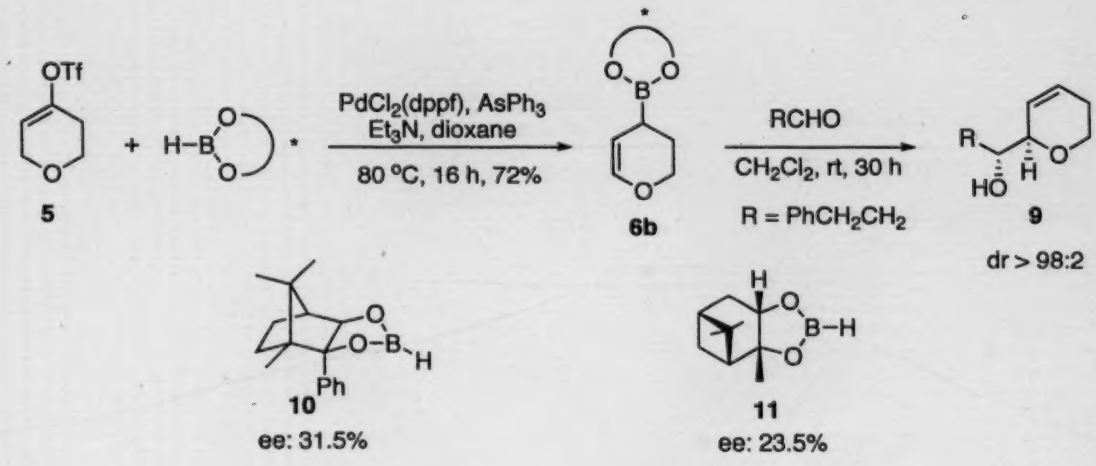
Alkenyl triflate **5** was prepared according to McMurry's procedure[10] and the product was obtained in good yield (Equation 3-2). Compound **5** is not stable at room temperature and thus needs a low-temperature storage.



Equation 3-2 Preparation of starting material **5**

3.2.2 Optimization process

Inspired by the success of chiral auxiliary approaches in the allylboration reaction, [11] we first tested two chiral boranes **10** and **11**. They were prepared according to the reported method.[12] When using achiral Pd catalyst and chiral borane **10** or **11**, the final allylboration product was obtained in good diastereoselectivity but poor enantioselectivity (Scheme 3-3).



Scheme 3-3 Chiral-borane approaches

Since the chiral borane approach did not provide promising results, we then changed our strategy by screening different chiral diphosphine ligands[13] using $Pd(OAc)_2$ as precatalyst, diisopropylethyl amine as base, and dioxane as solvent. Because compound **6a** is an α-substituted allylboronate and can transfer the chirality to the product completely,[6] we checked the ee of product **9** to evaluating the reactions. Screening a number of the commercially available chiral phosphine ligands revealed the superiority of Taniaphos ligand in terms of reaction conversion, chemical yield, diastereo- and enantioselectivity. JOSIPHOS, BINAP and DUPHOS, which were previously reported to provide high degrees of enantioselectivity in other known transformations, [13] appeared not to be competitive in this reaction. SYNPHOS and TUNEPHOS were also less efficient in this transformation. (Figure 3-1)

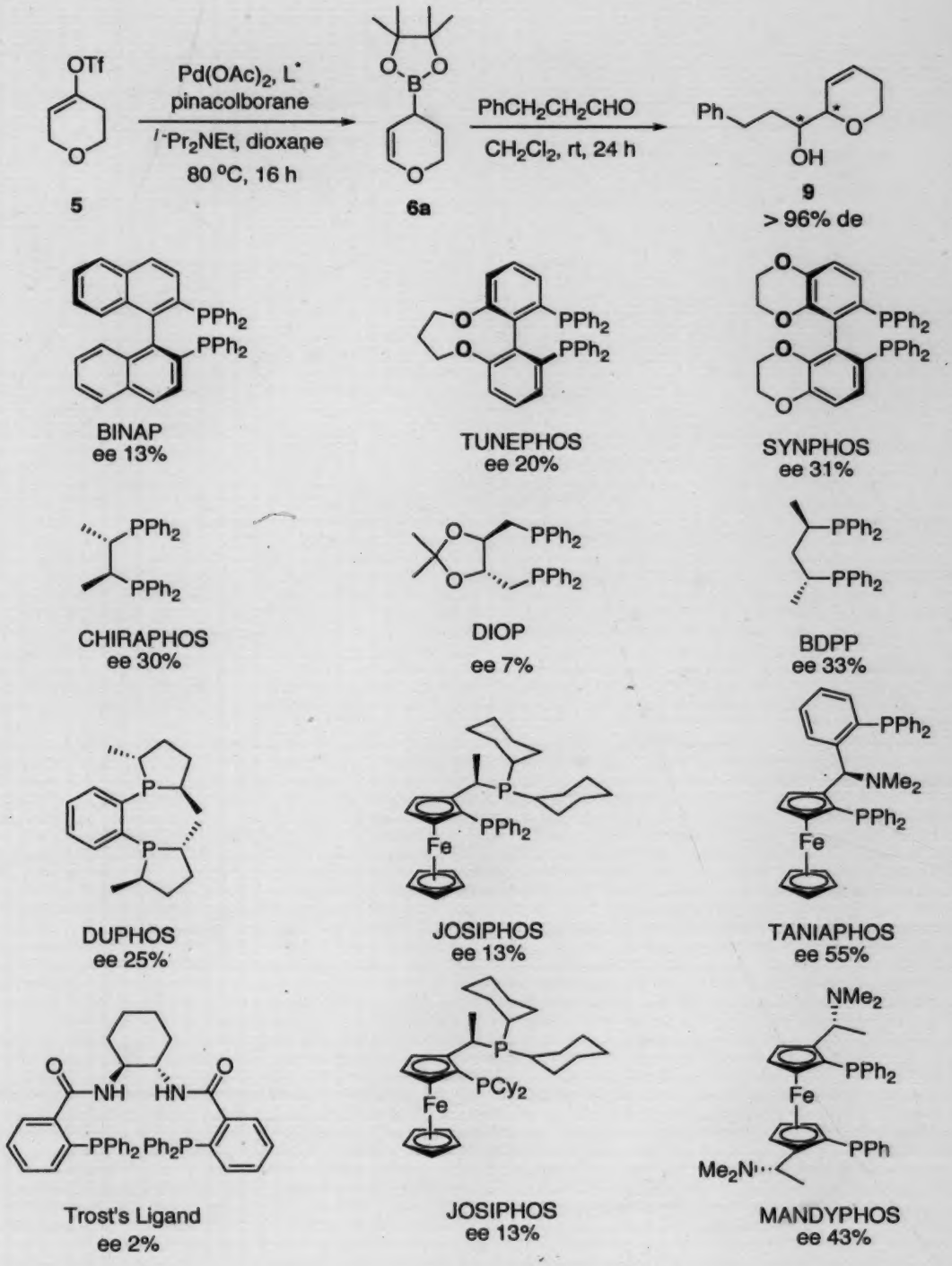


Figure 3-3 Chiral phosphine ligands screen

Our next effort was to explore the solvent effect on this reaction. Considering the price of the ligands, we chose the cheap but efficient BDPP ligand as a model ligand. The non-coordinating solvent, toluene, significantly improves the enantioselectivity of the reaction and provides an improved ee 53% compared with the original solvent, dioxane. Strong coordinating solvents, such as DMF and DMSO, decrease the enantioselectivity of the reaction (Table 3-1).

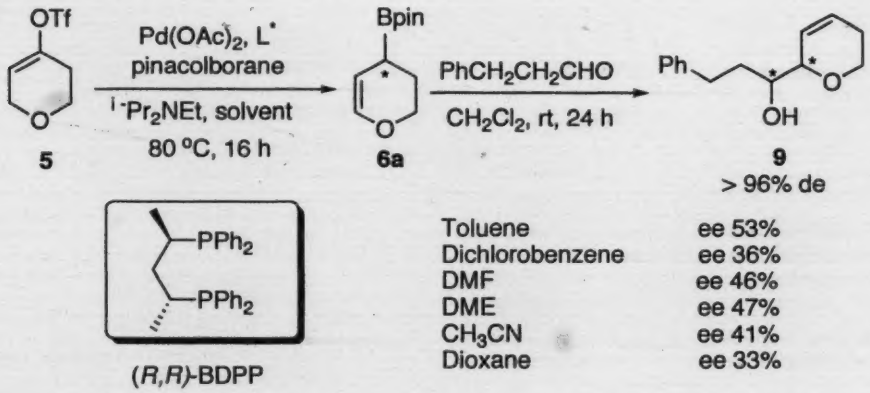


Table 3-1 Solvent screen in the isomerization reaction

As demonstrated in the asymmetric Heck reaction by several research groups, different bases can effect the enantioselectivity of the reaction.[14] We rationale that the enantioselectivity of our reaction may also be affected by different bases. Therefore, we explored different bases using the model BDPP ligand.

When we changed the base, the enantioselectivity of the final allylboration product did change. Screening of the base revealed that proton sponge **14** is the best in terms of reaction conversion and the enantioselectivity of the allylboration product (Table 3-2). Unfortunately, this result was later found to be irreproducible. Pyridine-type base **12** provides comparable enantioselectivity of the product, however, it affords poor conversion. Interestingly, 1,2,2,6,6-pentamethyl piperidine **13**, [13] which provides excellent enantioselectivity in several asymmetric Heck reactions, affords the final allylboration product in poor enantioselectivity (Table 3-2).

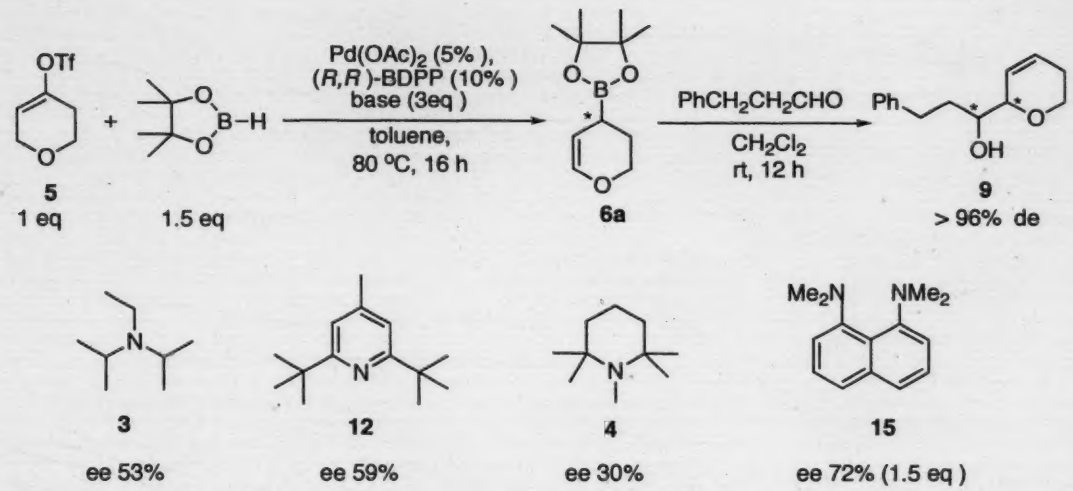
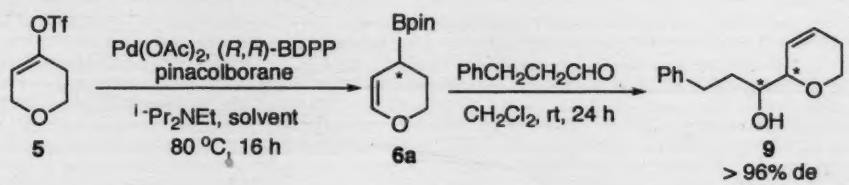


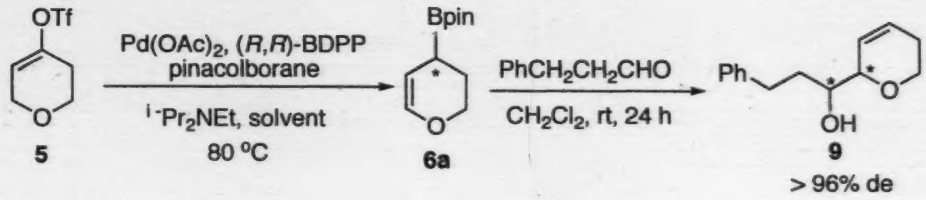
Table 3-2 Screening of different bases

The effect of temperature and reaction time were also investigated and the results are summarized in Table 3-3 and 3-4. As for the reaction temperature, it was found that 80 °C is crucial for achieving a good conversion. Lowering the temperature results in longer reaction time or no conversion. To check the reaction time, the reaction was quenched every four hours and the enantioselectivity of the final allylboration product was measured. The data indicated that racemization of the newly formed boronate **6** is unlikely.



	Conversion	ee
Condition 1 : 80 °C, 12 h	> 90%	53%
Condition 2 : 60 °C, 48 h	50%	55%
Condition 3 : 40 °C 48 h	0	

Table 3-3 Effect of reaction temperature



4 h	45% ee
8 h	44% ee
12 h	51% ee
16 h	53% ee

Table 3-4 Effect of reaction time

With the optimization information we obtained with the BDPP ligand, we then focused on the optimization of conditions with the Taniaphos ligand, which is a very expensive chiral ligand. Our first effort was to prepare enantiopure Taniaphos ligand. Based on Prof. Knochel's procedure, the chiral Taniaphos was synthesized successfully from the cheap starting material, ferrocene.[15] Pleasingly, with toluene as solvent and proton sponge as base, Taniaphos provided a significantly increased ee: 70%.

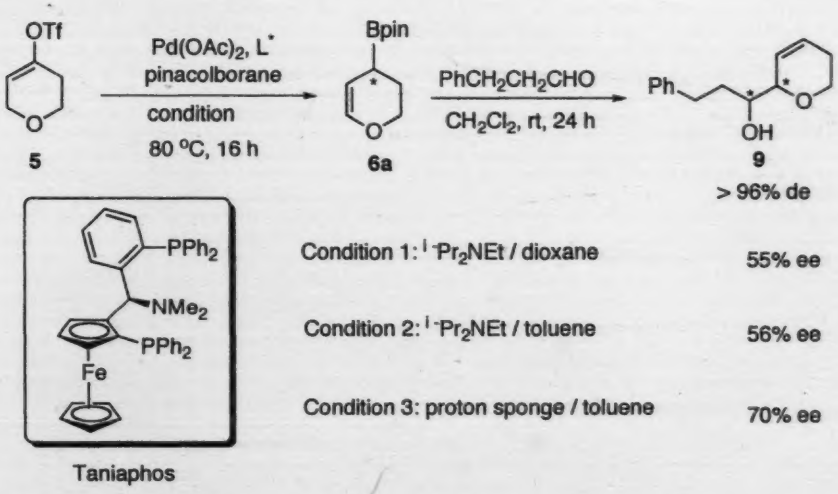
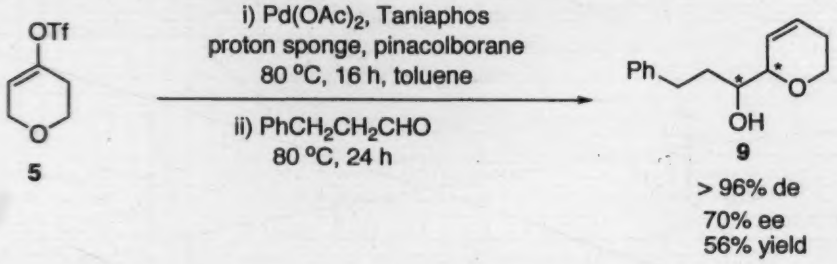


Table 3-5 Early optimization of Taniaphos ligand

A one-pot procedure was also tested and proved to be feasible. As showed in Equation 3-3, the final allylboration product was obtained in 56% yield and 70% ee.



Equation 3-3 One-pot isomerization/allylboration reaction

3.3 Conclusions and Future Direction

In summary, these preliminary results show that the Taniaphos ligand is very promising in the Pd-catalyzed asymmetric alkene isomerization/allylboration reaction, providing the final allylboration product with 56% yield and 70% ee. Future work in the Hall group will first focus on further improvements of the conversion and enantioselectivity for this reaction by screening more bases, additives, palladium sources and derivatives of Taniaphos ligand.

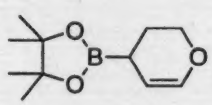
3.4 Experimental

3.4.1 General

Unless otherwise noted, all reactions were performed under an argon atmosphere using flame-dried glassware. Toluene, hexanes and CH_2Cl_2 were distilled over CaH_2. THF and Et_2O were distilled over sodium/benzophenone ketyl. All aldehydes were purified by Kugelrohr distillation prior to use. Thin layer chromatography (TLC) was performed on Silica Gel 60 F254 plates and was visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on 300, 400 or 500 MHz instruments. The residual solvent protons (^1H) or the

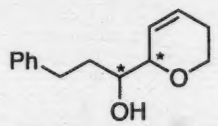
solvent carbons (^{13}C) were used as internal standards. Boron (^{11}B) NMR spectra are referenced to external $BF_3 \cdot OEt_2$. ^1H NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; qt, quartet of triplets; dd, doublet of doublets; dt, doublet of triplets; AB, AB quartet; m, multiplet. High resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared spectra and optical rotations were recorded by University of Alberta Spectral Services and combustion analyses were performed by the University of Alberta Micro-Analytical Lab. X-ray diffraction data were collected by the University of Alberta X-Ray Crystallography Laboratory. The enantiomeric excesses for all the compounds were determined using an HP 1100 HPLC system.

3.4.2 2-(3,4-dihydro-2*H*-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6a)



To a solution of $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol) and Taniaphos ligand (17.2 mg, 0.025 mmol) in toluene (2 mL) were added a solution of proton sponge (80 mg, 0.38 mmol) in toluene (2 mL), pinacolborane (55 μL, 0.375 mmol) and alkenyl triflate **5** (42 μL, 0.25 mmol). After stirring for 16 h at 80 °C, the mixture was quenched with water, extracted with ether and dried over anhydrous $MgSO_4$. The crude product was purified by flash chromatography to yield a colorless oil (5% EtOAc/hexanes, 60% yield). ^1H NMR ($CDCl_3$, 400 MHz): δ 6.38 (dd, J = 6.2, 2.4 Hz, 1H), 4.70 (dd, J = 6.2, 3.7 Hz, 1H), 4.04-3.90 (m, 2H), 2.00-1.85 (m, 2H), 1.84-1.76 (m, 1H), 1.24 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ142.9, 101.1, 83.3, 65.6, 24.8, 24.7, 24.3; IR (neat): cm^{-1} 2978, 2932, 2860, 1728, 1642, 1398, 1144; HRMS (ESP) calcd for $C_{11}H_{19}BO_3$: 210.1427; found: 210.1427.

3.4.3 1-(5,6-dihydro-2*H*-pyran-2-yl)-3-phenylpropan-1-ol (9)



To a solution of $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol) and Taniaphos ligand (17.2 mg, 0.025 mmol) in toluene (2 mL) were added a solution of proton sponge (80 mg, 0.38 mmol) in toluene (2 mL), pinacolborane (55 μL, 0.375 mmol) and vinyl triflate **5** (42 μL, 0.25 mmol). After stirring for 16 h at 80 °C, hydrocinnamaldehyde (40 μL, 0.5 mmol) was added. The reaction mixture was stirred for an additional 24 h at 80 °C, quenched with saturated $NaHCO_3$ solution and extracted with ether. The crude product was purified by flash chromatography to yield a colorless oil (10% EtOAc/hexane, 56% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.16 (m, 5H), 6.00-5.92 (m, 1H), 5.70-5.62 (m, 1H), 4.04-3.94 (m, 2H), 3.70 (ddd, J = 13.4, 9.3, 4.1 Hz, 1H), 3.60-3.50 (m, 1H), 2.95-2.66 (m, 2H), 2.40 (d, J = 4.3 Hz, 1H), 2.34-2.20 (m, 1H), 2.06-1.92 (m, 1H), 1.85 (ddd, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ142.2, 128.5, 128.3, 127.1, 126.6, 125.8, 76.7, 72.5, 63.1, 34.6, 31.9, 25.3; IR (neat): cm^{-1} 3442, 3027, 2921, 2859, 1496, 1454, 1086; HRMS (ESP) calcd for $C_{14}H_{18}O_2$: 218.1307; found: 218.1301. HPLC: Chiralcel OD, 50% *i*PrOH/Hexane, 0.50 mL/min., UV detection at 254 nm, Major peak at 9.4 min., minor peak at 8.0 min., 70% ee.

3.5 References:

1. Unger, F. M. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 323-325.
2. De Cree, J.; Geukens, H.; Leempoels, J.; Verhaegen, H. *Drug Dev. Res.* **1986**, *8*, 109-115.

3. (a) Burke, S. D.; Sametz, G. M. *Org. Lett.* **1999**, *1*, 71-74. (b) Trost, B. M.; Shen, H.; Dong, L.; Surivet, J.; Sylvain, C. *J. Am. Chem. Soc.* **2004**, *126*, 11966-11983.
4. Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9308-9309.
5. Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3059-3061.
6. Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123-130.
7. Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 1628-1629.
8. Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *Synthesis* **2000**, *6*, 778-780.
9. (a) Moriya, T.; Suzuki, A.; Miyaura, N. *Tetrahedron Lett.* **1995**, *36*, 1887-1890. (b) Ohmura, T.; Shirai, Y.; Yamamoto, Y.; Miyaura, N. *Chem. Commun.* **1998**, 1337-1338. (c) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390-13391. (d) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc.* **1984**, *106*, 5208-5217. (e) Tanaka, K.; Qiao, S.; Tobisu, M.; Lo, M.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 9870-9871.
10. Mc Murry, J. E.; Scott, W. J. *Tetrahedron Letts.* **1983**, *24*, 979-982.
11. (a) Brown, H. C.; Randad, R. S.; Bhat, K, S.; Zaidlewicz, M.; Racheria, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389-2392. (b) Short, R. P.; Masamune, S. *J. Am. Chem. Soc.* **1989**, *111*, 1892-1894. (c) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044-8049.
12. Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482-3485.
13. Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029-3070.
14. Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945-2964.
15. (a) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knechel, P. *Angew. Chem., Int. Ed.* **1998**, *38*, 3212-3215. (b) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164-7165.

Chapter 4 Development of Simple, Stable, and Versatile Double-Allylation Reagents for the Stereoselective Preparation of Skeletally Diverse Compounds

4.1 Introduction

Multifunctional reagents are very useful to prepare novel organic compounds. In fewer steps, they allow the formation of compounds with complex structures in high stereoselectivity. Among them, double allylation reagents are especially attractive because they can react with simple starting materials, such as ketones and aldehydes. Generally, double allylation reagents can be divided into three types according to the different positions of the metal atoms (Figure 4-1). To date, the design of double-allylation reagents based on boron has focused on Type I and Type II patterns.

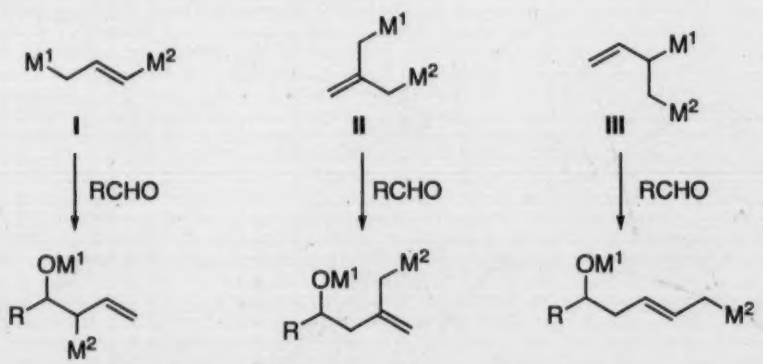
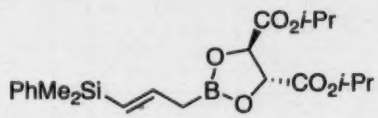


Figure 4-1 Three types of double-allylation reagents

There are several reported double allylation reagents based on boron and silicon. In 1990, Roush and co-workers first reported double allylation reagent **1**[1] (Figure 4-2), in which the silicon atom sits on the γ position of an allylboronate. Reagent **1** was used for the preparation of 1,2-*syn*-diols, polysubstituted tetrahydrofurans, and polysubstituted six-

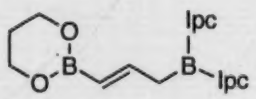
membered rings.[2] This reagent was also used successfully to synthesize natural product (+)-Bullatacin. [2] Despite its great versatility, the enantioselectivity of reagent **1** is low.



1

Figure 4-2 Diisopropyl 2-[(*E*)-γ-(dimethylphenylsilyl)]allyl-1,3,2-dioxaborolane-4,5-dicarboxylate

Shortly after the report of reagent **1**, the Roush group reported another kind of double allylation reagents, **2** and **3**, [3] in which a second boron atom sits on the γ position of an allylborane (Figure 4-3). This family of reagents can be used to synthesize 1,5-*syn* and 1,5-*anti*-diols in a one-pot procedure. The diastereoselectivity and yields are good to excellent for the formation of the products of double additions to two different aldehydes.[3]



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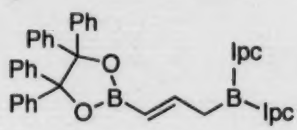
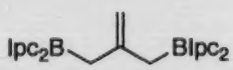


3

Figure 4-3 Diboron double-allylation reagents from Roush and co-workers

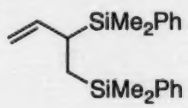
Based on a different design, Barrett and co-workers developed the double allylation reagent **4**, in which a borylmethyl group sits on the β position of an allylborane moiety (Figure 4-4). This reagent allows the formation of 1,5-*syn*-diols in high stereoselectivity.[4]



4

Figure 4-4 Diboron double-allylation reagent from Barrett and co-workers

Very recently, a racemic Type III reagent based on silicon, **5**, was reported by Sakai and co-workers[5] (Figure 4-5). This reagent can react with different kind of aldehydes to form polysubstituted tetrahydrofurans, however, the diastereoselectivity is poor.

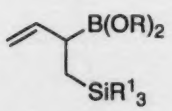


5

Figure 4-5 Disilicon double allylation reagent

4.2 Project Plan

We wanted to introduce a new type of double-allylation reagent, **6,** based on boron and silicon (Figure 4-6). Reagent **6** is an α-substituted allylboronate, anticipated to be stable and transfer the chirality to the products with near perfection.[9] Based on our design, we also anticipated that boron and silicon could be judiciously positioned to react independently with a variety of electrophiles.



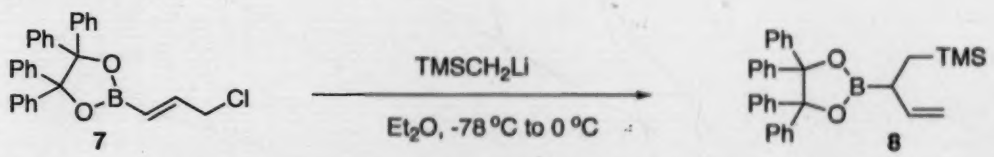
6

Figure 4-6 New design of double-allylation reagent

4.3 Results and Discussion

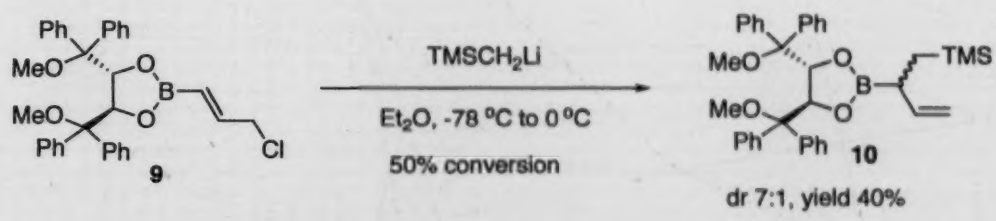
4.3.1 Preparation of reagents

We first tested the possibility to prepare a racemic reagent to prove our concept. Eventually, the racemic reagent **8** was synthesized using a vinylogous Matteson rearrangement.[6] Thus, treatment of **7** with $TMSCH_2Li$ in ether leads to product **8** in 40% yield (Equation 4-1).



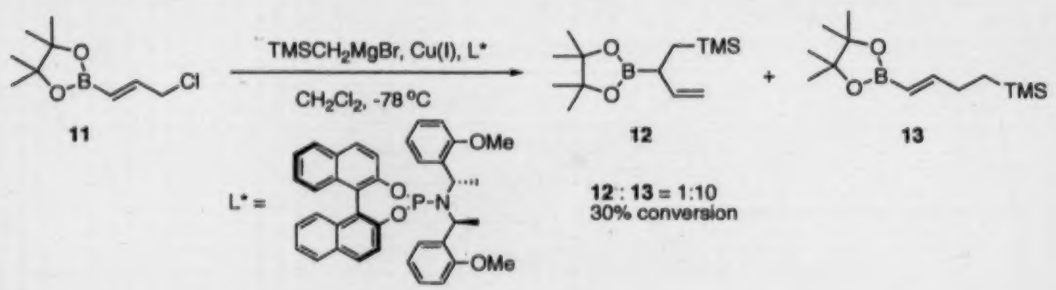
Equation 4-1 Synthesis of model reagent **8**

Encouraged by the success of making the racemic reagent **8**, we then focused on the preparation of an enantiopure reagent. An asymmetric vinylogous Matteson rearrangement using TADDOL as auxiliary was first tested in order to prepare optically pure α-trimethylsilylmethyl allylboronates (Equation 4-2). Treatment of **9** with $TMSCH_2Li$ led to product **10**, however, the diastereoselectivity is moderate and the conversion is poor. The poor selectivity may derive from the coordination of the Li ion with the methoxy group from the TADDOL unit.



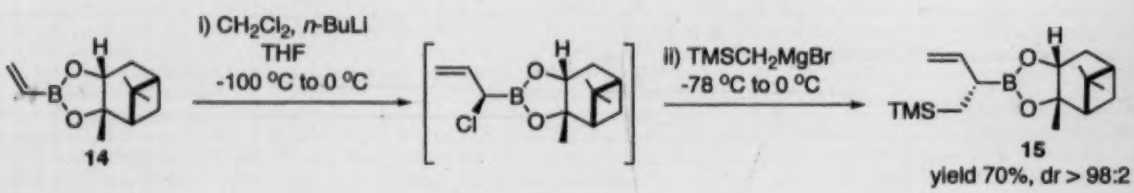
Equation 4-2 Asymmetric vinylogous Matteson rearrangement using TADDOL

Because a Cu-catalyzed asymmetric allylic alkylation (AAA) approach worked well to prepare α-substituted allylboronates for my labmate Lisa Carosi, [7] we also tested this strategy (Equation 4-3). Thus, an addition of $TMSCH_2MgBr$ to substrate **11** under the Cu (I)-catalyzed conditions afforded the branched allylboronate **12** and linear alkenylboronate **13**. Unfortunately, the regioselectivity favors the linear product **13** and the conversion is poor.



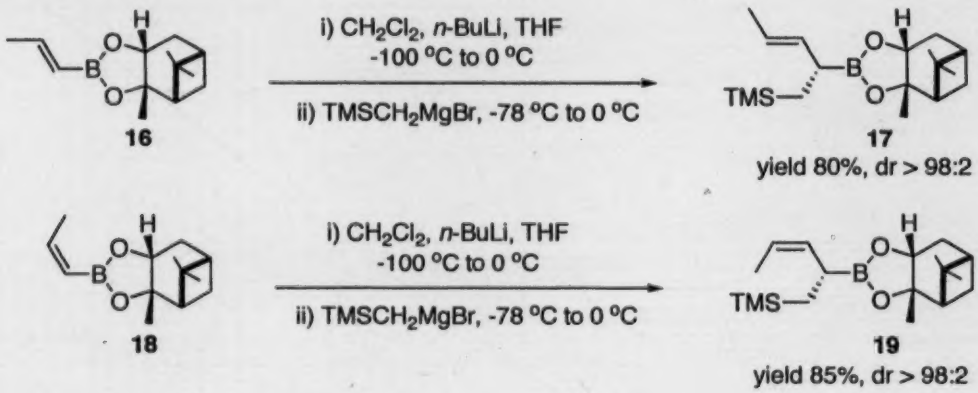
Equation 4-3 Cu-catalyzed AAA approach to prepare **12**

It was later found that the Matteson homologation reaction[6] is very efficient at preparing these α-trimethylsilylmethyl allylboronates. Thus, treatment of **14** with CH_2Cl_2 and *n*-BuLi at -100 °C, followed by addition of $TMSCH_2MgBr$ in a one-pot procedure leads to the final product **15** with a diastereomeric ratio (dr) of more than 98:2 (Equation 4-4). Interestingly, if this preparation was carried in two separated steps, the dr of the final product **15** will drop down to 80:20 due to the epimerization of intermediates during the purification step.[6] The one-pot procedure is crucial to achieve higher diastereoselectivity.



Equation 4-4 Preparation of **15** using the Matteson homologation reaction

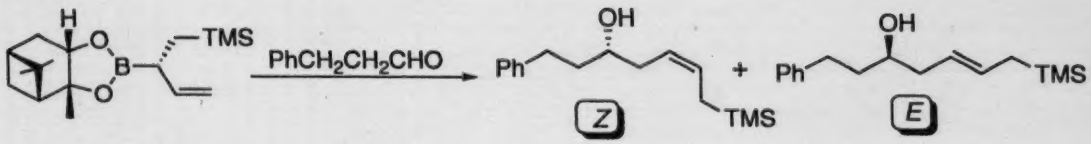
The *Z* and *E* crotyl reagents **17** and **19** were prepared via the same strategy. The products **17** and **19** were obtained with high dr and good yields as expected from the success of the simple reagent **15** (Equation 4-5).



Equation 4-5 Preparation of crotylboronates **17** and **19**

4.3.2 Results and discussion

With the desired reagents in hand, we tested their reactivity without any hesitate. Reagent **15** reacts with hydrocinnamaldehyde without Lewis acid catalysts to afford the corresponding homoallylic alcohol with a disappointingly poor *E*/*Z* ratio (Figure 4-7). In contrast, the low-temperature Lewis acid-catalyzed allylboration manifold[8] provided the products in very high *E*/*Z* selectivity and excellent enantioselectivities (Table 4-1). The outstanding *E* selectivity is very important for the practical use of reagent **15** because the *Z* isomer is epimeric at the carbinol[9, 10] and would require a separation in the situation of a lower selectivity. Generally, it is very difficult to separate these two isomers for bench chemist. This issue is avoided with the BF_3-promoted conditions, and remarkably, no-double allylation products from the further reaction of the allylic silane product were observed.

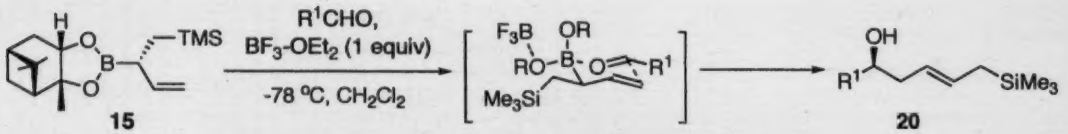


condition **1**: rt, 12 h, CH_2Cl_2 $Z/E = 3 : 1$

condition **2**: -78 °C, 12 h, BF_3-OEt_2 (1 equiv), CH_2Cl_2 $Z/E = 1 : 35$

Figure 4-7 Allylboration reaction using reagent **15**

The scope of aldehydes was also tested and we found that a wide range of aliphatic and unsaturated aldehydes are suitable substrates for reagent **15**. As depicted in table 4-1, the enantiofacial selectivity is controlled by the configuration of the reagent's α-carbon center and the preference for a pseudo-equatorial orientation of the -CH_2TMS substituent. The influence of the pinanedioxy unit is likely negligible.[11b] The high degree of *E*/*Z* selectivity can be tentatively explained by a late transition state involving coordination of the Lewis acid to a boronate oxygen.[8b, 11]

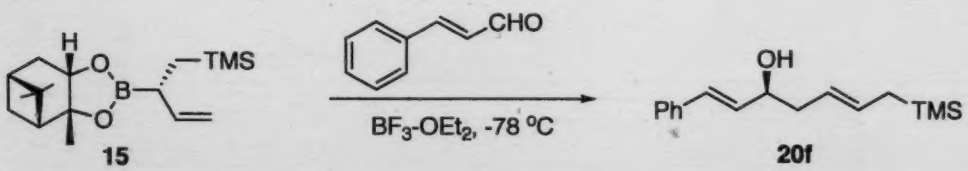


entry	R^1	product	yield(%)	E/Z	ee(%)
1	$Ph(CH_2)_2$	**20a**	77	>30:1	95
2	*n*-C_7H_{15}	**20b**	70	>30:1	98
3	*i*-Pr	**20c**	63	>30:1	96
4	$BnOCH_2$	**20d**	70	>25:1	91
5	Ph	**20e**	72	>30:1	95
6	(*E*)-PhCH=CH	**20f**	75	>30:1	79
7	(*E*)-MeCH=CH	**20g**	81	>30:1	96
8	(*n*-C_5H_{11})C≡C	**20h**	85	>30:1	95

Table 4-1 Scope of aldehydes in addition with reagent **15**

The moderate enantioselectivity from cinnamaldehyde is probably due to the epimerization of the corresponding homoallylic alcohol product **20f**. In order to test this

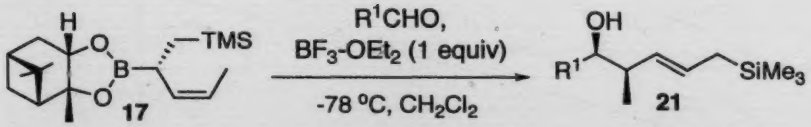
hypothesis, modified allylboration conditions using reagent **15** and cinnamaldehyde were tested. As the data showed in Table 4-2, Decreasing BF_3-OEt_2 loading (Entry 3 and 4) or stopping the reaction at an early stage (Entry 2) leads to an increase the ee of the product (Table 4-2).



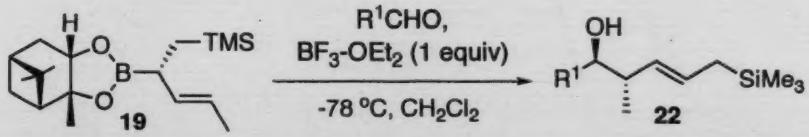
Entry	BF_3 Loading	reaction time	conversion	ee of product
1	100%	16 h	100%	78%
2	100%	4 h	45%	86%
3	30%	20 h	55%	91.1%
4	10%	20 h	33%	91.2%

Table 4-2 Modified conditions with cinnamaldehyde

Under the same conditions, the corresponding *Z* and *E* crotyl reagents **17** and **19** react with different aldehydes and afford the respective *syn* propionate products and *anti* diastereomers in high yields and high selectivity (Table 4-3).



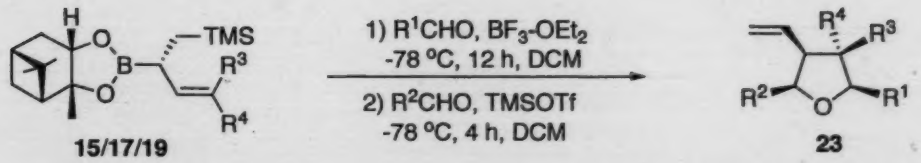
entry	R^1	Product	yield(%)	E/Z	*syn/anti*	ee(%)
1	$Ph(CH_2)_2$	**21a**	85	>40:1	>50:1	94
2	$BnOCH_2$	**21b**	90	>25:1	>30:1	96
3	Ph	**21c**	94	>40:1	>50:1	93



entry	R^1	Product	yield(%)	E/Z	*syn/anti*	ee(%)
1	$Ph(CH_2)_2$	**22a**	85	>40:1	>50:1	95
2	$BnOCH_2$	**22b**	80	>25:1	>40:1	98
3	Ph	**22c**	98	>40:1	>50:1	95

Table 4-3 Scope of aldehydes in addition with crotylreagents **17** and **19**

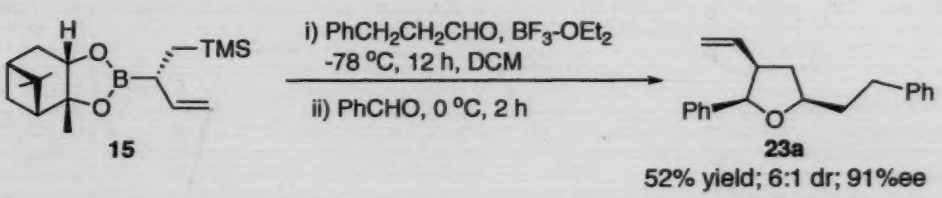
The potential versatility of reagents **15, 17** and **19** is linked to the rich chemistry of allylic silanes.[12] For an example, an intramolecular Sakurai condensation with aldehydes affords the all-*cis* substituted tetrahydrofurans with very high diastereo- and enantioselectivity. This approach allows the formation of diversified optically pure polysubstituted tetrahydrofurans **23** in two steps from simple aldehydes when using reagents **15, 17** and **19** (Table 4-4). These polysubstituted tetrahydrofurans are very common units in many natural products.



entry	1	R^1	R^2	R^3	R^4	Product	yield(%)	dr	ee(%)
1		$PhCH_2CH_2$	Ph	H	H	**23a**	75	25:1	93
2		Ph	$BnOCH_2$	H	H	**23b**	72	25:1	91
3		$PhCH_2CH_2$	$BnOCH_2$	Me	H	**23c**	72	27:1	93
4		$PhCH_2CH_2$	$BnOCH_2$	H	Me	**23d**	76	28:1	95
5		$PhCH_2CH_2$	n-C_7H_{15}	H	H	**23e**	82	25:1	94

Table 4-4 Preparation of polysubstituted tetrahydrofurans

In order to further improve the efficiency in the synthesis of polysubstituted tetrahydrofurans, a one-pot procedure was also investigated. Thus, treatment of reagent **15** with hydrocinnamaldehyde under BF_3 catalysis for 12 hours, followed by the addition of benzaldehyde with the temperature increasing from -78 °C to 0 °C, leads to the final product **23a** in moderate yield and diastereoselectivity and excellent ee (Equation 4-6).



Equation 4-6 One-pot procedure to prepare optically pure furan **23a**

The diastereoselectivity in the all-*cis* furan formation is explained by the pseudo-diequatorial arrangement of R^1 and R^2 to minimize steric interactions in the transition state model (Figure 4-8). A similar model was also proposed by other research groups.[13]

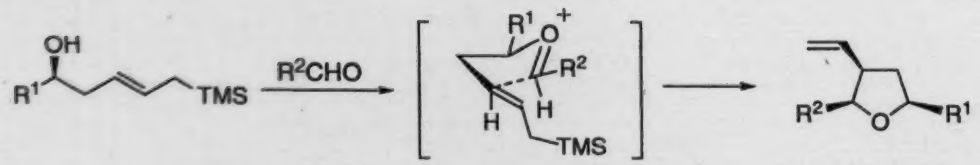
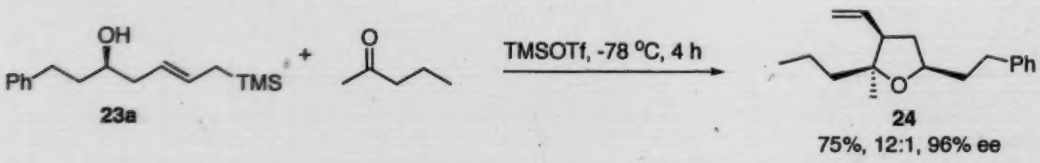


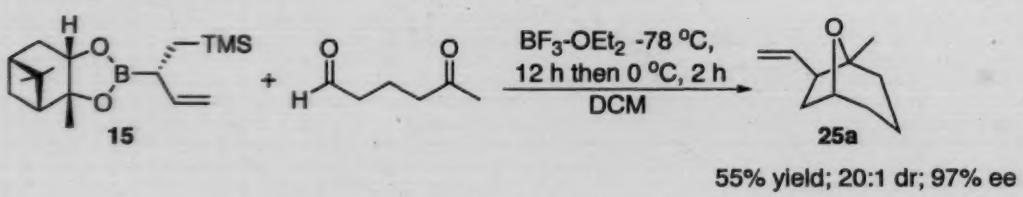
Figure 4-8 Transition state for the furan formation

Interestingly, the unprecedented use of ketones in this reaction provides 1,1,2,4-tetrasubstituted tetrahydrofurans such as **24** in high yields and acceptable diastereoselectivity and excellent ee (Equation 4-7).



Equation 4-7 Reaction of **23a** with a model ketone

The use of dicarbonyl substrates can provide several opportunities for accessing large carbocycles and other ring systems. As showed in equation 4-8, a cascade reaction happens when reagent **15** reacts with 4-oxopentanal (Equation 4-8). The resulting oxabicyclic product **25a** was obtained in high stereoselectivity. The relative stereochemistry was assigned based on TROSY NMR technique.



Equation 4-8 Preparation of oxabicyclic compound **25a**

Mechanistically, an intramolecular oxonium formation followed by addition of the allylic silane moiety is proposed (Figure 4-9).

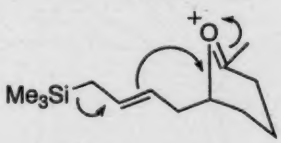
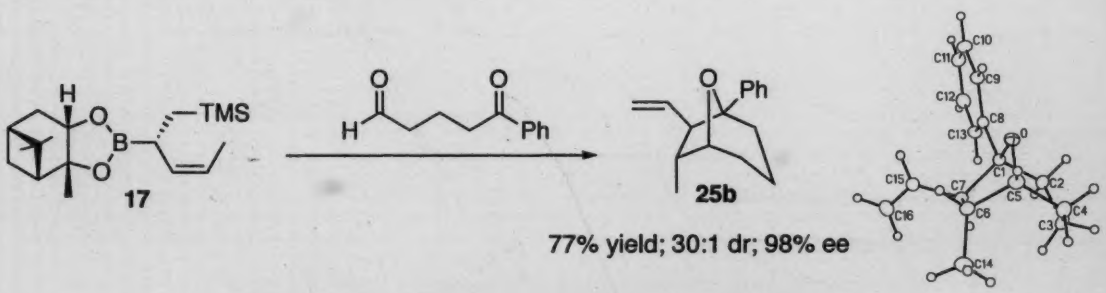


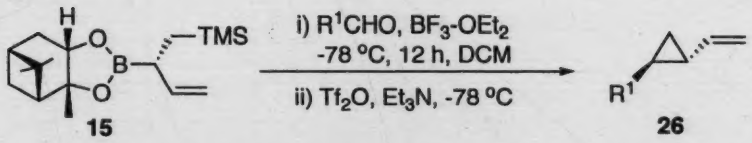
Figure 4-9 Mechanism for the formation of oxabicycle compound

When reagent **19** reacts with a ketoaldehyde under the same condition, a similar cascade reaction happens. The final product **25b** was isolated as a solid with high stereoselectivity (Equation 4-9). The X-ray crystallographic structure matches the proposed compound structure based on NMR analysis.



Equation 4-9 Preparation of oxabicyclic compound **25b**

Vinylcyclopropanes are very useful building blocks in organic synthesis.[14] It was demonstrated by Prof. Taylor that functionalized allylsilanes can be transformed to vinylcyclopropanes, [15] however, it is very difficult to prepare these functionalized allylsilanes directly in optically pure form. Using our family of reagents **15**, **17** and **19**, we can synthesize these silanes with high stereocontrol from simple aldehydes starting materials. Thus, as showed in Table 4-5, we can prepare optically pure vinylcyclopropanes **26** in two steps from aldehydes using reagent **15**.

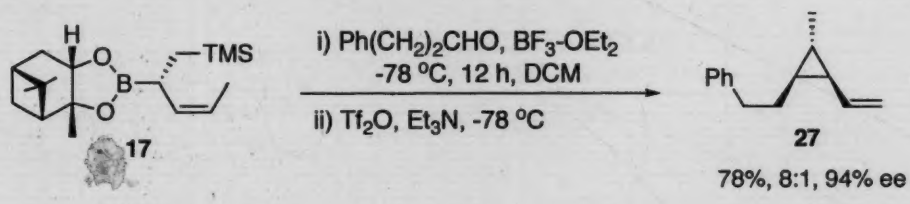


15 26

R^1	Product	yield(%)	dr	ee(%)
$PhCH_2CH_2$	**26a**	81	20:1	93
n-C_7H_{15}	**26b**	72	15:1	95
$BnOCH_2$	**26c**	56	11:1	90

Table 4-5 Preparation of vinylcyclopropanes

Trisubstituted vinylcyclopropanes can also be prepared using reagents **17** and **19**. For example, addition of hydrocinnamaldehyde to reagent **19**, followed by reacting with Tf_2O leads to the trisubstituted cyclopropane product **27** (Equation 4-10).



17 27

78%, 8:1, 94% ee

Equation 4-10 Preparation of trisubstituted cyclopropane **27**

4.4 Conclusions and Future Directions

In summary, we have disclosed a new family of simple and efficient double-allylation reagents: the α-trimethylsilylmethyl allylboronate **15** and the corresponding crotylboronates **17** and **19**. These stable bimetallic reagents add onto a wide range of aldehydes to afford direct access to hydroxyl-functionalized allylic silanes in very high *E*/*Z* selectivity and excellent enantioselectivity. The use of the novel Lewis acid-catalyzed allylboration manifold was key to the overall selectivity of this process. Through the hydroxyl-

functionalized allylsilane products, reagents **15**, **17** and **19** can be exploited in chemodivergent synthesis of various compound classes such as propionate units, polysubstituted tetrahydrofurans, vinylcyclopropanes, and large carbocycles.

Future directions of this project in the Hall group will involve exploring more applications of reagents **15**, **17** and **19** and catalytic methods to prepare these reagents.

4.5 Experimental

4.5.1 General information

Unless otherwise noted, all reactions were performed under an argon atmosphere using flame-dried glassware. Toluene, hexanes and CH_2Cl_2 were distilled over CaH_2. THF and Et_2O were distilled over sodium/benzophenone ketyl. All aldehydes were purified by Kugelrohr distillation prior to use. Thin layer chromatography (TLC) was performed on Silica Gel 60 F254 plates and was visualized with UV light and $KMnO_4$ stain. NMR spectra were recorded on 300, 400 or 500 MHz instruments. The residual solvent protons (^1H) or the solvent carbons (^{13}C) were used as internal standards. Boron NMR spectra are referenced to external $BF_3{\cdot}OEt_2$. ^1H NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; qt, quartet of triplets; dd, doublet of doublets; dt, doublet of triplets; AB, AB quartet; m, multiplet. High resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared spectra and optical rotations were recorded by University of Alberta Spectral Services and combustion analyses were performed by the University of Alberta Micro-Analytical Lab. X-ray diffraction data were collected by the University of Alberta X-Ray Crystallography Laboratory.

4.5.2 Determination of enantiomeric excess, diatereoselectivity and E/Z ration.

The enantiomeric excesses for all the compounds were determined using an HP 1100 HPLC system. The enantiomeric excesses for compounds **20b, 20c, 20g** and **20h** were determined on the corresponding phenylisocyanate adduct using an HP 1100 HPLC system. The enantiomeric excesses for compounds **26** and **27** were determined on the corresponding alcohols (By transforming the alkene to alcohol[16]) using an HP 1100 HPLC system. The enantiomeric excesses for compound **25a** were determined on the corresponding alcohol phenylisocyanate adduct (By transforming the alkene to alcohol[1]) using an HP 1100 HPLC system. Details of chromatographic conditions are indicated under each compound. Columns Chiralcel AD-RH, Chiralcel OD-RH, Chiralcel OD, and Chiralcel AD were purchased from Chiral Technologies Inc.. Racemic compounds were prepared in the same manner using the pinacol boronate derivatives. The diatereoselectivity for compounds **20, 21, 22, 23, 24, 25, 26** and **27** was determined by ^{1}H NMR. The E/Z ratios for compounds **20, 21** and **22** were determined by ^{1}H NMR using TMS peaks of crude mixtures.

4.5.3 Preparation of alkenylboronic ester precursors

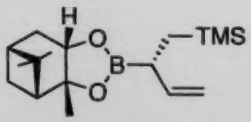
A solution of representative the alkenylboronic acids (*E* and *Z*-1-propenylboronic acids were purchased from Aldrich, and vinyl boronic acid was prepared according to a reported procedure [17]) (6 mmol) and (1*R*, 2*R*, 3*S*, 5*R*)-(-)-pinanediol (5 mmol) in 10 ml of anhydrous THF was stirred 12 h at room temperature. The solvent was then removed and the product was purified by flash chromatography (78% yield) to obtain analytically pure alkenyl boronate ester, which had identical spectroscopic data to that reported. [17]

4.5.4 Preparation of reagents 15, 17 and 19.[18]

A solution of 0.5 mL of dichloromethane in 10 ml of anhydrous THF was cooled to -100 °C using 95% ethanol/liquid nitrogen slush bath. *n*-BuLi (3.33 mL, 5 mmol) was added through the inside wall of reaction flask over 5 min. The reaction mixture was stirred for 20 min and then vinylboronic ester (5 mmol) in 3 mL of anhydrous THF was added in one portion. After 2 min, the reaction mixture was warmed up to 0 °C and stirred for an additional 40 min. At this stage, the reaction mixture was cooled down to -78 °C and freshly

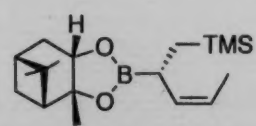
prepared $TMSCH_2MgBr$ (5 mmol) in THF (6 mL) was added slowly. The reaction mixture was stirred 3 h at -78 °C, 12 h at room temperature, then quenched with NH_4Cl solution, extracted with ether, dried over anhydrous Na_2SO_4, filtered and purified by flash chromatography.

Reagent 15



Flash chromatography (hexanes) yielded a colorless oil (1.06 g, 70%). TLC (25% EtOAc/Hexane, $KMnO_4$): Rf 0.90; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.89 (ddd, J = 16.8, 10.0, 8.4 Hz, 1H), 5.02 (ddd, J = 17.2, 1.6, 1.6 Hz, 1H), 4.90 (d, J = 10.0 Hz, 1H), 4.28 (dd, J = 8.8, 2.0 Hz 1H), 2.37-2.31 (m, 1H), 2.22-2.18 (m, 1H), 2.08-2.06 (m, 1H), 1.99-1.97 (m, 1H), 1.92-1.82 (m, 2H), 1.40 (s, 3H), 1.29 (s, 3H), 1.13 (d, J = 10.8 Hz, 1H), 0.88 (dd, J = 14.4, 7.6 Hz, 1H), 0.85 (s, 3H), 0.70 (dd, J = 14.8, 7.6 Hz, 1H), 0.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ142.2, 112.2, 85.5, 77.8, 51.4, 39.4, 38.2, 35.4, 28.5, 27.1, 26.2, 24.0, 17.0, -1.0; ^{11}B NMR ($CDCl_3$, 128 MHz) δ 32.6; IR (neat): cm^{-1} 2950, 1627, 1386, 1246, 859; HRMS (EI, *m/z*) calcd for $C_{17}H_{31}O_2BSi$: 306.2186; found: 306.2181 [M^+]. $[\alpha]^{25}_D$ -18.98 (c = 0.60, $CHCl_3$).

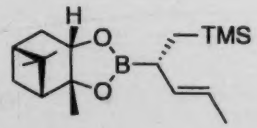
Reagent 19



Flash chromatography (hexanes) yielded a colorless oil (1.31 g, 85%). TLC (25% EtOAc/Hexane, $KMnO_4$): Rf 0.90; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.40-5.30 (m, 2H), 4.25 (dd, J = 8.7, 2.0 Hz, 1H), 2.36-2.28 (m, 1H), 2.24-2.14 (m, 2H), 2.04 (dd, J = 5.3, 5.3 Hz, 1H), 1.92-1.86 (m, 1H), 1.82 (ddd, J = 14.5, 3.3, 2.0 Hz 1H), 1.62 (d, J = 4.9 Hz, 1H), 1.38 (s, 3H), 1.28 (s, 3H), 1.12 (d, J = 10.9 Hz, 1H), 0.88 (dd, J = 14.6, 6.8 Hz, 1H), 0.86 (s, 3H),

0.65 (dd, J = 14.6, 8.3 Hz, 1H), -0.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ134.5, 121.4, 85.3, 77.7, 51.5, 39.4, 38.2, 35.5, 28.5, 27.1, 26.1, 24.0, 18.2, 13.1, -1.0;
IR (neat): cm^{-1}: 2917, 1442, 1375, 1247, 1078; HRMS (EI, *m/z*) calcd for $C_{10}H_{17}O_5B$: 320.2343; found: 320.2335 [M$^+$]. $[\alpha]^{25}_D$ -9.79 (c = 0.40, $CHCl_3$).

Reagent 17

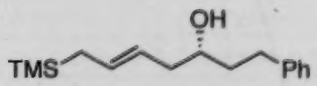


Flash chromatography (hexanes) yielded a colorless oil (1.25 g, 80%). TLC (25% EtOAc/Hexane, $KMnO_4$): Rf 0.90; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.46-5.34 (m, 2H), 4.25 (dd, J = 8.7, 2.0 Hz, 1H), 2.36-2.28 (m, 1H), 2.22-2.14 (m, 2H), 2.04 (dd, J = 5.2, 5.2 Hz, 1H), 1.92-1.86 (m, 2H), 1.82 (ddd, J = 14.4, 3.2, 2.0 Hz 1H), 1.63 (d, J = 4.7 Hz, 1H), 1.38 (s, 3H), 1.28 (s, 3H), 1.12 (d, J = 10.8 Hz, 1H), 0.85 (dd, J = 14.7, 7.6 Hz, 1H), 0.84 (s, 3H), 0.65 (dd, J = 14.6, 7.6 Hz, 1H), -0.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 134.5, 122.9, 85.4, 77.7, 51.4, 39.4, 38.2, 35.5, 28.5, 27.1, 26.1, 24.0, 18.0, 17.8, -1.0; IR (neat): cm^{-1}: 2919, 1448, 1377, 1250, 849; HRMS (EI, *m/z*) calcd for $C_{10}H_{17}O_5B$: 320.2343; found: 320.2339 [M$^+$]. $[\alpha]^{25}_D$ -11.75 (c = 0.45, $CHCl_3$).

4.5.5 General procedure for the allylboration reaction.

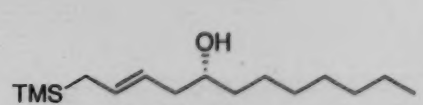
At -78 °C, to a flame-dried round bottom flask, was added the boron reagent (0.2 mmol), aldehyde (0.2 mmol) and 1 mL of dichloromethane. The mixture was stirred for 5 min, after which BF_3-Et_2O (0.2 mmol) was added. The reaction mixture was stirred further 12 h at -78 °C and then quenched with an aqueous $NaHCO_3$ solution, extracted with ether, dried over anhydrous Na_2SO_4 and filtered. The products were purified by flash chromatography.

4.5.6 (*R*,*E*)-7-(trimethylsilyl)-1-phenylhept-5-en-3-ol (20a)



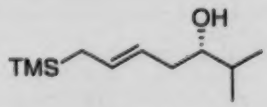
Flash chromatography (5% EtOAc/hexanes) yielded a colorless oil (41 mg, 77%). TLC (25% EtOAc/Hexane, $KMnO_4$): Rf 0.4; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.16 (m, 5H), 5.56 (ddd, J = 15.6, 8.1, 8.1 Hz, 1H), 5.24 (ddd, J = 15.1, 7.3, 7.3 Hz, 1H), 3.60 (ddddd, J = 4.4, 3.9, 3.9, 3.9, 3.9 Hz, 1H), 2.86-2.64 (m, 2H), 2.32-2.26 (m, 1H), 2.15-2.06 (m, 1H), 1.82-1.74 (m, 2H), 1.65 (d, J = 3.9 Hz, 1H), 1.48 (d, J = 8.1 Hz, 2H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ142.3, 131.0, 128.4, 128.3, 125.7, 123.9, 70.3, 41.1, 38.4, 32.1, 23.1, -2.0; IR (neat): cm^{-1} 3360, 3026, 2952, 1604, 1248; HRMS (ESP) calcd for $C_{16}H_{26}OSiNa$: 285.1645; found: 285.1643. $[\alpha]^{25}_D$ +2.25 (c = 1.10, $CHCl_3$). HPLC: Chiralcel OD, 10% *i*PrOH/Hexane, 0.50 mL/min., UV detection at 210 nm., major peak at 12.9 min., minor peak at 10.2 min., 95% ee.

4.5.7 (*R*,*E*)-1-(trimethylsilyl)dodec-2-en-5-ol (20b)



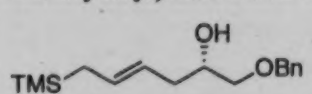
Flash chromatography (5% EtOAc/hexanes) yielded a colorless oil (36 mg, 70%), which gave satisfactory analytical data. TLC (25% EtOAc/ hexanes, $KMnO_4$): Rf 0.60; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.54 (ddd, J = 15.6, 8.1, 8.1 Hz, 1H), 5.26 (ddd, J = 15.5, 7.3, 7.3 Hz, 1H), 3.58 (ddddd, J = 4.3, 3.9, 3.9, 3.9, 3.9 Hz, 1H), 2.28-2.20 (m, 1H), 2.10-2.00 (m, 1H), 1.60 (d, J = 3.9 Hz, 1H), 1.48 (d, J = 8.2 Hz, 2H), 1.48-1.22 (m, 10H), 0.88 (dd, J = 6.7, 6.7 Hz, 3H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 130.7, 124.2, 71.1, 40.9, 36.7, 331.8, 29.7, 29.3, 25.7, 23.0, 22.6, 14.1, -2.0; IR (neat): cm^{-1} 3349, 2955, 2928, 2856, 1248; HRMS (ESP) calcd for $C_{15}H_{32}OSiNa$: 279.2115; found: 279.2113. $[\alpha]^{25}_D$ -3.5 (c = 0.9, $CHCl_3$). HPLC: Chiralcel OD, 10% *i*PrOH/Hexane, 0.50 mL/min., UV detection at 210 nm, major peak at 15.9 min., minor peak at 12.2 min., 98% ee.

4.5.8 (*S*,*E*)-2-methyl-7-(trimethylsilyl)hept-5-en-3-ol (20c)



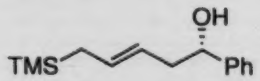
Flash chromatography (5% EtOAc/Hexanes) yielded a colorless oil (25 mg, 63%), which gave satisfactory analytical data. TLC (15% EtOAc/hexanes, $KMnO_4$): Rf 0.60; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.54 (ddd, *J* = 15.6, 8.0, 8.0 Hz, 1H), 5.26 (ddd, *J* = 15.1, 7.8, 7.8 Hz, 1H), 3.32-3.27 (m, 1H), 2.30-2.23 (m, 1H), 2.04 (ddd, *J* = 13.9, 8.5, 8.5 Hz, 1H), 1.67 (dddd, *J* = 13.4, 6.7, 6.7, 6.7 Hz, 1H), 1.58 (d, *J* = 3.7 Hz, 1H), 1.48 (d, *J* = 8.1 Hz, 2H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 130.6, 124.6, 75.7, 37.9, 32.9, 23.0, 18.8, 17.6, -2.0; IR (neat): cm^{-1} 3390, 2956, 1404, 1248; HRMS (ESP) calcd for $C_{15}H_{32}OSiNa$: 223.1489; found: 223.1487. $[\alpha]^{25}_D$ -8.55 (c = 0.2, $CHCl_3$). HPLC: Chiralcel OD, 10% *i*PrOH/Hexane, 0.50 mL/min., UV detection at 210 nm, major peak at 15.6 min., minor peak at 12.5 min., 96% ee.

4.5.9 (*S*,*E*)-1-(benzyloxy)-6-(trimethylsilyl)hex-4-en-2-ol (20d)



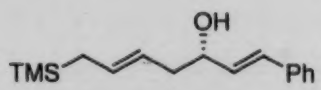
Flash chromatography (8% EtOAc/hexanes) yielded a colourless oil (39 mg, 70%), which gave satisfactory analytical data. TLC (25% EtOAc/hexanes, $KMnO_4$): Rf 0.40; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.26 (m, 5H), 5.50 (ddd, *J* = 15.6, 8.0, 8.0 Hz, 1H), 5.24 (ddd, *J* = 15.2, 7.1, 7.1 Hz, 1H), 4.56 (s, 2H), 3.80 (ddddd, *J* = 4.4, 3.9, 3.9, 3.9, 3.9 Hz, 1H), 3.52 (dd, *J* = 9.5, 3.4 Hz, 1H), 3.37 (dd, *J* = 9.4, 7.3 Hz, 1H), 2.26 (d, *J* = 3.4 Hz 1H), 2.20 (d, *J* = 6.2, 6.2 Hz, 2H), 1.45 (d, *J* = 8.0 Hz, 2H), -0.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.1, 130.1, 128.4, 127.7, 127.7, 123.5, 74.0, 73.4, 70.3, 37.0, 22.9, -2.0; IR (neat): cm^{-1} 3455, 3029, 2953, 2900, 1454, 1248; HRMS (ESP) calcd for $C_{16}H_{26}O_2SiNa$: 301.1594; found: 301.1594. $[\alpha]^{25}_D$ -1.00 (c = 1.10, $CHCl_3$). HPLC: Chiralcel OD, 5% *i*PrOH/hexane, 0.50 mL/min., UV detection at 210 nm, major peak at 15.5 min., minor peak at 17.7 min., 91% ee.

4.5.10 (*S*,*E*)-5-(trimethylsilyl)-1-phenylpent-3-en-1-ol (20e)



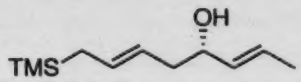
Flash chromatography (5% EtOAc/hexanes) yielded a colorless oil (34 mg, 72%), which gave satisfactory analytical data. TLC (25% EtOAc/Hexane, $KMnO_4$): Rf 0.40; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.24 (m, 5H), 5.56 (ddd, J = 15.7, 8.1, 8.1 Hz, 1H), 5.24 (ddd, J = 15.3, 7.2, 7.2 Hz, 1H), 4.68 (ddd, J = 8.0, 4.9, 3.2 Hz, 1H), 2.54-2.38 (m, 2H), 2.06 (d, J = 3.3 Hz 1H), 1.48 (d, J = 8.4 Hz, 1H), -0.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.0, 131.3, 128.3, 127.3, 125.8, 123.6, 73.5, 43.0, 23.1, -2.0; IR (neat): cm^{-1} 3363, 3028, 2953, 2899, 1658, 1247; HRMS (ESP) calcd for $C_{14}H_{22}OSiNa$: 257.1332; found: 257.1332. $[\alpha]^{25}_D$ -23.15 (c = 1.1, $CHCl_3$). HPLC: Chiralcel OD, 10% *i*PrOH/Hexane, 0.50 mL/min., UV detection at 210 nm, major peak at 9.8 min., minor peak at 9.1 min., 95% ee.

4.5.11 (*S*,1*E*,5*E*)-7-(trimethylsilyl)-1-phenylhepta-1,5-dien-3-ol (20f)



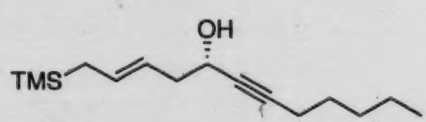
Flash chromatography (5% EtOAc/hexanes) yielded a colorless oil (39 mg, 75%), which gave satisfactory analytical data. TLC (25% EtOAc/hexanes, $KMnO_4$): Rf 0.25; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.22 (m, 5H), 6.60 (d, J = 16.0 Hz, 1H), 6.25 (dd, J = 16.0, 6.2 Hz 1H), 5.58 (ddd, J = 15.8, 8.1, 8.1 Hz, 1H), 5.28 (ddd, J = 15.1, 7.7, 7.7 Hz, 1H), 4.32-4.24 (m, 1H), 2.44-2.26 (m, 2H), 1.8 (d, J = 4.0 Hz, 2H), 1.50 (d, J = 8.1 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.9, 131.9, 131.3, 130.1, 128.5, 127.5, 126.4, 123.2, 72.0, 41.2, 23.1, -2; IR (neat): cm^{-1} 3398, 3027, 2953, 2899, 1678, 1626, 1450, 1248; HRMS (ESP) calcd for $C_{16}H_{24}OSiNa$: 283.1490; found 283.1486. HPLC: Chiralcel OD, 10% *i*PrOH/Hexane, 0.5 mL/min.; UV detection at 210 nm, major peak at 18.6 min., minor peak at 12.4 min., 79% ee.

4.5.12 (*S*,2*E*,6*E*)-8-(trimethylsilyl)octa-2,6-dien-4-ol (20g)



Flash chromatography (5% EtOAc/hexanes) yielded a colorless oil (32 mg, 81%), which gave satisfactory analytical data. TLC (25% EtOAc/hexanes, $KMnO_4$): Rf 0.40; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.68 (ddddd, J = 15.2, 6.5, 6.5, 6.5, 1.0 Hz, 1H), 5.56-5.46 (m, 2H), 5.24 (ddd, J = 15.1, 7.2, 7.2 Hz, 1H), 4.05 (ddd, J = 11.5, 6.3, 6.3 Hz, 1H), 3.32-3.27 (m, 1H), 2.30-2.16 (m, 2H), 1.70 (ddd, J = 6.4, 1.5, 0.7 Hz, 3H), 1.62 (d, J = 3.7 Hz, 1H), 1.47 (d, J = 8.1 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 133.5, 130.7, 126.7, 123.6, 72.1, 41.1, 23.0, 17.7, -2.0; IR (neat): cm^{-1} 3344, 2955, 2917, 1439, 1248; HRMS (ESP) calcd for $C_{11}H_{22}OSiNa$: 221.1332; found: 221.1333. $[\alpha]^{25}_D$ -4.77 (c = 0.90, $CHCl_3$). HPLC: Chiralcel OD, 1% *i*PrOH/Hexane, 0.5 mL/min., UV detection at 210 nm, major peak at 19.2 min., minor peak at 24.5 min., 96% ee.

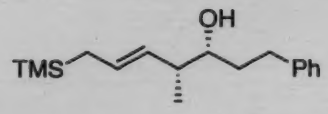
4.5.13 (*S*,*E*)-1-(trimethylsilyl)dodec-2-en-6-yn-5-ol (20h)



Flash chromatography (5% EtOAc/Toluene) yielded a colorless oil (43 mg, 85%), which gave satisfactory analytical data. TLC (25% EtOAc/Hexane, $KMnO_4$): Rf 0.50; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.56 (ddd, J = 15.6, 8.1, 8.1 Hz, 1H), 5.30 (ddd, J = 15.1, 7.3, 7.3 Hz, 1H), 4.32 (ddddd, J = 6.1, 6.1, 6.1, 1.8, 1.8 Hz, 1H), 2.38 (dd, J = 7.0, 7.0 Hz 2H), 2.20 (dddd, J = 7.0, 7.0, 1.9, 1.9 Hz 2H), 1.82 (d, J = 6.1 Hz 1H), 1.52 (m, 2H), 1.48 (d, J = 7.5 Hz, 2H), 1.40-1.28 (m, 4H), 0.90 (dd, J = 6.9 Hz, 3H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 131.4, 122.6, 85.6, 80.9, 62.3, 41.6, 31.0, 28.4, 23.1, 22.2, 18.7, 14.0, -2.0; IR (neat): cm^{-1} 3352, 2955, 2933, 2861, 2226, 1248; HRMS (ESP) calcd for $C_{15}H_{28}OSiNa$: 275.1802; found: 275.1804. $[\alpha]^{25}_D$ -8.70 (c = 1.20, $CHCl_3$). HPLC: Chiralcel OD, 2.5%

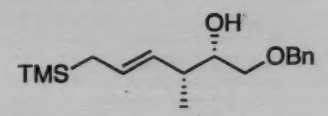
*i*PrOH/hexane, 0.50 mL/min., UV detection at 210 nm, major peak at 8.4 min., minor peak at 16.6 min., 95% ee.

4.5.14 (*E*,3*R*,4*R*)-4-methyl-7-(trimethylsilyl)-1-phenylhept-5-en-3-ol (21a)



Flash chromatography (5% EtOAc/toluene) yielded a colorless oil (47 mg, 85%). TLC (25% EtOAc/hexanes, $KMnO_4$): Rf 0.50; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.18 (m, 5H), 5.50 (ddd, *J* = 15.6, 8.1, 8.1 Hz, 1H), 5.15 (dddd, *J* = 15.2, 7.9, 0.9, 0.9 Hz, 1H), 4.55 (dddd, *J* = 11.1, 5.6, 5.6, 3.0 Hz 1H), 2.90 (ddd, *J* = 13.8, 10.3, 5.1 Hz 1H), 2.65 (ddd, *J* = 13.8, 9.9, 6.6 Hz 1H), 2.26 (dddd, *J* = 14.1, 6.9, 6.9, 6.9 Hz 1H), 1.90-1.80 (m, 1H), 1.70-1.60 (m, 1H), 1.46-1.38 (m, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.4, 130.4, 128.5, 128.3, 127.9, 125.7, 74.6, 43.1, 35.8, 32.5, 22.9, 15.6, -2.0 IR (neat): cm^{-1} 3375, 3028, 2955, 1454, 1248; HRMS (ESP) calcd for $C_{17}H_{29}OSi$: 277.1982; found: 277.1984. $[\alpha]^{25}_D$ +14.10 (c = 0.50, $CHCl_3$). HPLC: Chiralcel OD, 10% *i*PrOH/Hexane, 0.50 mL/min., UV detection at 254 nm, Major peak at 12.4 min., minor peak at 9.5 min., 94% ee.

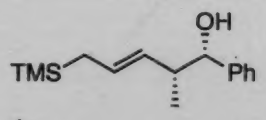
4.5.15 (*E*,2*S*,3*R*)-1-(benzyloxy)-3-methyl-6-(trimethylsilyl)hex-4-en-2-ol (21b)



Flash chromatography (10% EtOAc/hexanes) yielded a colorless oil (53 mg, 90%). TLC (15% EtOAc/Hexane, $KMnO_4$): Rf 0.30; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.26 (m, 5H), 5.45 (ddd, *J* = 15.7, 8.1, 8.1 Hz, 1H), 5.15 (dddd, *J* = 15.2, 8.3, 1.3, 1.3 Hz, 1H), 4.55 (s, 2H), 3.60-3.55 (m, 1H), 3.37 (dd, *J* = 10.0, 8.4 Hz, 1H), 2.34 (d, *J* = 3.6 Hz, 1H), 2.25 (dddd, *J* = 14.6, 7.4, 7.4, 7.4 Hz 1H), 1.40 (dd, *J* = 8.1, 1.2 Hz, 2H), 1.06 (d, *J* = 6.8 Hz, 3H), -0.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.1, 130.2, 128.4, 127.7, 127.7, 127.2, 74.0, 73.4,

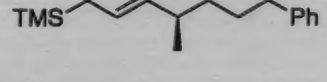
73.1, 40.6, 22.8, 17.0, -2.0; IR (neat): cm^{-1} 3466, 2956, 2900, 2870, 1454, 1248; HRMS (ESP) calcd for $C_{17}H_{28}O_2SiNa$: 315.1751; found: 315.1753. $[\alpha]^{25}_D$ +22.83 (c = 0.30, $CHCl_3$). HPLC: Chiralcel OD, 10% *i*PrOH/Hexane, 0.50 mL/min., UV detection at 210 nm, Major peak at 10.0 min., minor peak at 11.1 min., 96% ee.

4.5.16 (*E*,1*S*,2*R*)-2-methyl-5-(trimethylsilyl)-1-phenylpent-3-en-1-ol (21c)



Flash chromatography (5% EtOAc/hexanes) yielded a colorless oil (47 mg, 94%), which gave satisfactory analytical data. TLC (25% EtOAc/hexanes, $KMnO_4$): Rf 0.50; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.22 (m, 5H), 5.45 (ddd, *J* = 15.6, 8.1, 8.1 Hz, 1H), 5.15 (dddd, *J* = 15.2, 10.5, 1.3, 1.3 Hz, 1H), 4.55 (dd, *J* = 5.6, 4.0 Hz 1H), 2.56 (dddd, *J* = 13.2, 6.9, 6.9, 6.9 Hz 1H), 1.98 (m, 1H), 1.44 (d, *J* = 8.0 Hz, 2H), 0.98 (d, *J* = 6.9 Hz, 3H), -0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.8, 129.9, 128.1, 128.0, 127.2, 126.6, 77.7, 44.0, 22.9, 15.4, -2; IR (neat): cm^{-1} 3393, 2956, 2875, 1453, 1248; HRMS (ESP) calcd for $C_{15}H_{24}OSiNa$: 271.1489; found: 271.1487. $[\alpha]^{25}_D$ -12.15 (c = 0.6, $CHCl_3$). HPLC: Chiralcel OD, 2.5% *i*PrOH/Hexane, 0.5 mL/min., UV detection at 254 nm, major peak at 15.2 min., minor peak at 13.7 min., 93% ee.

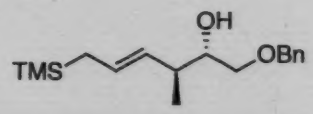
4.5.17 (*E*,3*R*,4*S*)-4-methyl-7-(trimethylsilyl)-1-phenylhept-5-en-3-ol (22a)



Flash chromatography (10% EtOAc/hexanes) yielded a colorless oil (47 mg, 85%). TLC (25% EtOAc/Hexane, $KMnO_4$): Rf 0.50; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.18 (m, 5H), 5.50 (ddd, *J* = 15.8, 8.1, 8.1 Hz, 1H), 5.15 (dddd, *J* = 15.3, 8.6, 1.2, 1.2 Hz, 1H), 3.38-3.30 (m, 1H), 2.86 (ddd, *J* = 13.8, 10.5, 5.1 Hz 1H), 2.65 (ddd, *J* = 13.7, 10,0, 6.4 Hz 1H), 2.15 (dddd, *J* = 13.4, 6.4, 6.4, 6.4 Hz 1H), 1.90-1.80 (m, 1H), 1.74-1.64 (m, 1H), 1.71 (d, *J* = 3.7

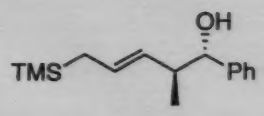
Hz, 1H), 1.47 (dd, J = 8.0, 1.2 Hz, 2H), 1.01 (d, J = 6.9 Hz, 3H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.5, 130.1, 129.2, 128.5, 128.3, 125.7, 74.3, 43.8, 36.1, 32.2, 23.0, 17.1, -2.0; IR (neat): cm^{-1} 3410, 2955, 2874, 1454, 1248; HRMS (ESP) calcd for $C_{17}H_{28}OSiNa$: 299.1802; found 299.1803. $[\alpha]^{25}_D$ -10.45 (c = 0.20, $CHCl_3$). HPLC: Chiralcel OD, 10% *i*PrOH/Hexane, 0.50 mL/min., UV detection at 210 nm, Major peak at 10.7 min., minor peak at 8.5 min., 95% ee.

4.5.18 (*E*,2*S*,3*S*)-1-(benzyloxy)-3-methyl-6-(trimethylsilyl)hex-4-en-2-ol (22b)



Flash chromatography (10% EtOAc/hexanes) yielded a colourless oil (38 mg, 58%). TLC (25% EtOAc/Hexane, $KMnO_4$): Rf 0.40; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.18 (m, 5H), 5.50 (ddd, J = 15.8, 8.1, 8.1 Hz, 1H), 5.15 (dddd, J = 15.3, 8.6, 1.2, 1.2 Hz, 1H), 3.38-3.30 (m, 1H), 2.86 (ddd, J = 13.8, 10.5, 5.1 Hz 1H), 2.65 (ddd, J = 13.7, 10,0, 6.4 Hz 1H), 2.15 (dddd, J = 13.4, 6.4, 6.4, 6.4 Hz 1H), 1.90-1.80 (m, 1H), 1.74-1.64 (m, 1H), 1.71 (d, J = 3.7 Hz, 1H), 1.47 (dd, J = 8.0, 1.2 Hz, 2H), 1.01 (d, J = 6.9 Hz, 3H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 1142.5, 130.1, 129.2, 128.5, 128.3, 125.7, 74.3, 43.8, 36.1, 32.2, 23.0, 17.1, -2.0; IR (neat): cm^{-1} 3410, 2955, 2874, 1454, 1248; HRMS (ESP) calcd for $C_{17}H_{28}OSiNa$: 299.1802; found: 299.1803. $[\alpha]^{25}_D$ -23.40 (c = 0.5, $CHCl_3$). HPLC: Chiralcel OD, 10% *i*PrOH/Hexane, 0.50 mL/min., UV detection at 210 nm, Major peak at 9.5 min., minor peak at 11.3 min., 98% ee.

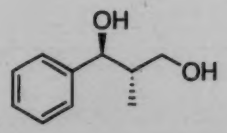
4.5.19 (*E*,1*S*,2*S*)-2-methyl-5-(trimethylsilyl)-1-phenylpent-3-en-1-ol (20c)



Flash chromatography (10% EtOAc/hexanes) yielded a colorless oil (49 mg, 98%). TLC (25% EtOAc/Toluene, $KMnO_4$): Rf 0.5; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.26 (m, 5H), 5.45 (ddd, J = 15.8, 8.1, 8.1 Hz, 1H), 5.15 (dddd, J = 15.2, 8.6, 1.1, 1.1 Hz, 1H), 4.26 (dd, J = 8.2, 2.1 Hz 1H), 2.40 (dddd, J = 14.8, 6.9, 6.9, 6.9 Hz 1H), 2.27 (d, J = 2.2 Hz, 1H), 1.52 (dd, J = 8.1, 1.2 Hz, 2H), 0.84 (d, J = 6.9 Hz, 3H), 0.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.6, 130.4, 130.0, 128.1, 127.5, 127.0, 78.0, 46.0, 23.1, 17.4, -2.0; IR (neat): cm^{-1} 3430, 3030, 2956, 2895, 1453, 1248; HRMS (ESP) calcd for $C_{15}H_{24}OSiNa$: 271.1489; found: 271.1490. $[\alpha]^{25}_D$ -183.28 (c = 0.4, $CHCl_3$). HPLC: Chiralcel OD, 10% *i*PrOH/Hexane, 0.50 mL/min., UV detection at 210 nm, Major peak at 13.6 min., minor peak at 15.2 min., 95% ee.

4.5.20 Determination of absolute stereochemistry of compound 22c.

Compound **18** was transformed to the known 2-methyl-1-phenylpropane-1,3-diol,[16] which has $[\alpha]^{25}_D$ -29.89 (c = 1.5, $CHCl_3$). Based on the comparison of the sign of optical rotation reported in the literature [16] to the one obtained from compound **18**, the absolute stereochemistry is as follow.

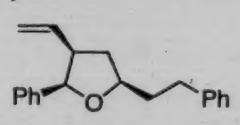


(1*S*,2*S*)-2-methyl-1-phenylpropane-1,3-diol

4.5.21 General procedure for the synthesis of polysubstituted tetrahydrofurans.

At -78 °C, to a flame-dried round bottom flask, was added **20** (0.2 mmol), aldehyde (0.2 mmol) and 2 mL of dichloromethane. The mixture was stirred for 5 min, and then TMSOTf (0.1 mmol) was added. The reaction mixture was stirred further 4 h at -78 °C and then quenched with an aqueous $NaHCO_3$ solution, extracted with ether, dried over anhydrous Na_2SO_4, and filtered. The products were purified by flash chromatography. The relative stereochemistry was assigned based on TROESY NMR technique.

4.5.22 Tetrahydro-5-phenethyl-2-phenyl-3-vinylfuran (23a)

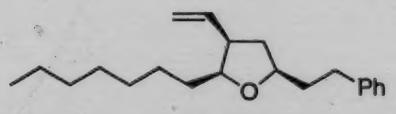


Flash chromatography (5% EtOAc/Hexane) gave the pure product as a colourless oil (75% yield), which gave satisfactory analytical data. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.20 (m, 10H), 5.20 (ddd, J = 17.0, 10.0, 8.7 Hz, 1H), 5.06 (d, J = 8.1 Hz, 1H), 4.90 (ddd, J = 17.1, 1.9, 1.0 Hz, 1H), 4.78 (dd, J = 10.0, 1.8 Hz, 1H), 4.56 (dddd, J = 11.1, 7.3, 5.5, 5.5 Hz 1H), 3.2 (dddd, J = 8.3, 8.3, 8.3, 8.3 Hz 1H), 2.92-2.74 (m, 2H), 2.25-2.15 (m, 2H), 2.05-1.97 (m, 1H), 1.60 (ddd, J = 12.3, 9.2, 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.0, 140.4, 138.6, 128.4, 128.4, 127.8, 127.0, 126.8, 125.8, 114.9, 83.2, 78.7, 48.9, 38.3, 37.3, 32.7; IR (neat): cm^{-1} 3027, 2927, 2861, 1495, 1453, 1053; HRMS (EI) calcd for $C_{20}H_{22}O$: 278.1671; found: 278.1666. HPLC: Chiralcel OD, 10% *i*PrOH/Hexane, 0.50 mL/min., UV detection at 210 nm, major peak at 19.2 min., minor peak at 14.0 min., 93% ee.

4.5.23 "One-pot" three-component reaction to form 23a

At -78 °C, to a flame-dried round bottom flask, was added boron reagent **15** (0.2 mmol), hydrocinnamaldehyde (0.2 mmol) and 1 mL of dichloromethane. The mixture was stirred for 5 min, and then BF_3-Et_2O (0.2 mmol) was added. The reaction mixture was stirred further 12 h at -78 °C and then benzaldehyde (0.2 mmol) was added to the reaction mixture. The reaction mixture was stirred at -78 °C for 2 h followed by 0 °C for 4 h, then quenched with an aqeous $NaHCO_3$ solution, extracted with ether, dried over anhydrous Na_2SO_4 and filtered. The products were purified by flash chromatography. Compound **5** was obtained with dr 6:1, 91% ee.

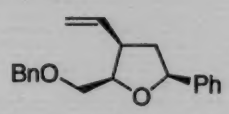
4.5.24 2-heptyl-tetrahydro-5-phenethyl-3-vinylfuran (23e)



Flash chromatography (5% EtOAc/Hexane) gave the pure product as a colourless oil (82% yield), which gave satisfactory analytical data. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.16 (m, 5H), 5.83-5.73 (m, 1H), 5.03-4.98 (m, 2H), 3.86-3.76 (m, 2H), 2.86-2.64 (m, 3H), 2.20 (ddd, J = 12.8, 8, 6.8 Hz, 1H), 2.03-1.94 (m, 1H), 1.86-1.78 (m, 1H), 1.50-1.20 (m, 12H), 0.92-0.86 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.2, 138.8, 128.4, 128.3, 125.7, 114.9, 81.7, 77.8,

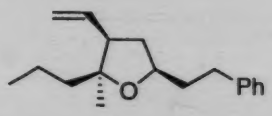
46.8, 38.2, 38.2, 32.7, 31.8, 31.8, 29.7, 29.3, 26.4, 22.7, 14.1; IR (neat): cm^{-1} 2926, 2855, 1454, 1050; HRMS (EI) calcd for $C_{21}H_{32}O$: 300.2453; found: 300.2450. HPLC: Chiralcel OD, 1% *i*PrOH/Hexane, 0.50 mL/min., UV detection at 210 nm, major peak at 19.2 min., minor peak at 14.0 min., 94% ee.

4.5.25 2-((benzyloxy)methyl)-tetrahydro-5-phenyl-3-vinylfuran (23b)



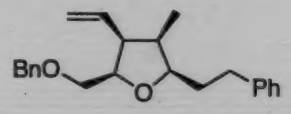
Flash chromatography (2.5% EtOAc/Hexane) gave the pure product as a colourless oil (72% yield), which gave satisfactory analytical data. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42-7.26 (m, 10H), 5.85 (ddd, J = 17.1, 10.0, 10.0 Hz, 1H), 5.10 (ddd, J = 17.1, 1.8, 1.0 Hz, 1H), 5.05 (ddd, J = 10.1, 1.8, 0.7 Hz, 1H), 4.95 (dd, J = 9.7, 6.0 Hz, 1H), 4.58 (d, J = 1.8 Hz 1H), 4.33-4.28 (m, 1 H), 3.64 (dd, J = 10.3, 4.0 Hz, 1H), 3.58 (dd, J = 10.2, 5.4 Hz, 1H), 3.15 (dddd, J = 8.7, 8.7, 8.7, 8.7 Hz 1H), 2.40 (ddd, , J = 13.1, 7.0, 7.0 Hz, 1H), 1.90 (ddd, J = 12.3, 9.7, 9.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.4, 138.4, 136.9, 128.3, 128.2, 127.7, 127.5, 127.3, 126.1, 116, 81.0, 80.6, 73.4, 71.2, 46.9, 41.1; IR (neat): cm^{-1} 3065, 2863, 1640, 1453, 1090; HRMS (ESP) calcd for $C_{20}H_{22}O_2Na$: 317.1512; found: 317.1514. $[\alpha]^{25}_D$ -56.13 (c = 0.60, $CHCl_3$). HPLC: Chiralcel OD, 5% *i*PrOH/Hexane, 0.50 mL/min., UV detection at 210 nm, major peak at 15.4 min., minor peak at 13.4 min., 91% ee.

4.5.26 (2*S*,3*R*,5*R*)-tetrahydro-2-methyl-5-phenethyl-2-propyl-3-vinylfuran (24)



Flash chromatography (5% EtOAc/hexanes) gave the pure product as a colourless oil with dr improving to >25:1 (75% yield), which gave satisfactory analytical data. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.16 (m, 5 H), 5.78 (ddd, J = 18.3, 10.2, 8.2 Hz, 1H), 5.10-5.0 (m, 2H), 4.05-3.97 (m, 1H), 2.80-2.55 (m, 3H), 2.12 (ddd, J = 12.3, 5.9, 5.9 Hz, 1H), 1.97-1.87 (m, 1H), 1.82-1.72 (m, 1H), 1.64 (ddd, J = 11.5, 11.5, 9.6 Hz, 1H 2H), 1.54-1.23 (m, 4H), 1.22 (s, 3H), 0.91 (dd, J = 7.1, 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.3, 137.4, 128.3, 128.3, 125.7, 115.7, 83.9. 76.9, 55.0, 40.0, 39.0, 37.9, 32.6, 25.1, 16.9, 14.9; IR (neat): cm^{-1} 3081, 3002, 2958, 2871, 1639, 1455, 1050; HRMS (EI) calcd for $C_{18}H_{26}O$: 258.1984; found: 258.1979. HPLC: Chiralcel OD, Hexane, 0.50 mL/min., UV detection at 210 nm, major peak at 17.4 min., minor peak at 16.0 min., 96% ee.

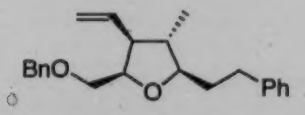
4.5.27 2-((benzyloxy)methyl)-tetrahydro-4-methyl-5-phenethyl-3-vinylfuran (23c)



Flash chromatography (2.5% EtOAc/Hexane) gave the pure product as a colourless oil with dr >25:1 (72% yield), which gave satisfactory analytical data. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.18 (m, 10H), 5.71 (ddd, J = 16.3, 10.6, 10.6 Hz, 1H), 5.10-5.02 (m, 2H), 4.63 (d, J = 12.3 Hz, 1H), 4.58 (d, J = 12.3 Hz, 1H), 4.12 (dd, J = 11.4, 6.0 Hz 1H), 3.95 (ddd, J = 11.7, 7.2, 4.6 Hz, 1 H), 3.55-3.52 (m, 2H), 2.94-2.82 (m, 2H), 2.65 (ddd, J = 16.3, 10.0, 6.2 Hz 1H), 2.48-2.38 (m, 1H), 1.86-1.69 (m, 2H), 0.87 (d, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.4, 138.5, 134.9, 128.4, 128.3, 128.3, 127.7, 125.7, 117.6, 80.5, 79.6, 73.3, 71.1, 51.1, 39.9, 34.0, 33.1, 10.9; IR (neat): cm^{-1} 2919, 2858, 1602, 1453, 1085; HRMS (ESP)

calcd for $C_{23}H_{28}O_2Na$: 359.1982; found: 359.1978. $[\alpha]^{25}_D$ +3.95 (c = 0.50, $CHCl_3$). HPLC: Chiralcel OD, Hexane, 1.00 mL/min., UV detection at 210 nm, major peak at 5.5 min., minor peak at 7.0 min., 93% ee.

4.5.28 (2*R*,3*S*,4*R*,5*R*)-2-((benzyloxy)methyl)-tetrahydro-4-methyl-5-phenethyl-3-vinylfuran (23d)



Flash chromatography (5% EtOAc/Hexane) gave the pure product as a colourless oil with dr>25:1 (75% yield), which gave satisfactory analytical data. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.18 (m, 10H), 5.71 (ddd, *J* = 17.4, 9.5, 9.5 Hz, 1H), 5.10-5.02 (m, 2H), 4.58 (s, 2H), 4.16 (ddd, *J* = 8.9, 5.2, 3.9 Hz 1H), 3.53 (dd, *J* = 10.3, 4.0 Hz, 1 H), 3.50-3.44 (m, 2H), 2.94-2.84 (m, 1H), 2.76-2.68 (m, 1H), 2.50 (dd, *J* = 9.3, 9.3 Hz, 1H), 1.98-1.69 (m, 3H), 0.93 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.5, 136.6, 128.4, 128.3, 127.6, 127.4, 125.7, 116.9, 85.3, 79.5, 73.3, 71.3, 55.2, 44.2, 36.1, 32.6, 15.1; IR (neat): cm^{-1} 2919, 2858, 1602, 1453, 1085; HRMS (ESP) calcd for $C_{23}H_{28}O_2Na$: 359.1982; found: 359.1986. $[\alpha]^{25}_D$ -2.76 (c = 0.70, $CHCl_3$). HPLC: Chiralcel OD, Hexane, 1.00 mL/min., UV detection at 210 nm, major peak at 5.2 min., minor peak at 6.6 min., 95% ee.

4.5.29 General procedure for the synthesis of compounds 26.

At -78 °C, to a flame-dried round bottom flask, was added **20** (0.2 mmol), 2,6-lutidine (0.2 mmol) and 2 mL of dichloromethane. The mixture was stirred for 2 min, and then Tf_2O (0.2 mmol) was added followed by Hunig's base (1 mmol). The reaction mixture was slowly warmed up to room temperature. After removing the solvent, the product was purified by flash chromatography. The relative stereochemistry for cyclopropanes was assigned based on coupling constants and NOE NMR experiments.[15]

4.5.30 1-(2-((1*S*,2*R*)-2-vinylcyclopropyl)ethyl)benzene (23a)

Flash chromatography (Hexane) yielded a colourless oil (81% yield), which gave satisfactory analytical data. TLC (25% EtOAc/toluene, $KMnO_4$): Rf 0.90; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.17 (m, 5H), 5.40 (ddd, J = 17.1, 10.2, 8.7 Hz, 1H), 5.02 (dd, J = 17.1, 1.76 Hz, 1H), 4.85 (dd, J = 10.2, 1.8 Hz, 1H), 2.72 (dd, J = 7.6, 7.6 Hz, 1H), 1.64-1.56 (m, 2H), 1.2 (dddd, J = 8.7, 8.7, 4.5, 4.5 Hz, 1H), 0.85-0.75 (m, 1H), 0.58 (ddd, J = 8.3, 4.7, 4.7 Hz, 1H), 0.54 (ddd, J = 8.3, 5.6, 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.3, 141.9, 128.5, 128.2, 125.7, 111.2, 35.8, 35.7, 22.6, 20.7, 14.0; IR (neat): cm^{-1} 2954, 1610, 1246; HRMS (EI) calcd for $C_{13}H_{14}$: 170.1096; found: 170.1098. $[M^+]$-2H. $[\alpha]^{25}_D$ +27.09 (c = 0.2, $CHCl_3$). HPLC: Chiralcel OD, 10% *i*PrOH/hexane, 1.00mL/min., UV detection at 254 nm, major peak at 6.7 min., minor peak at 7.82 min., 93% ee.

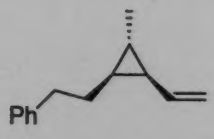
4.5.31 (1*S*,2*R*)-1-heptyl-2-vinylcyclopropane (26b)

Flash chromatography (Hexane) yielded a colourless oil (72% yield), which gave satisfactory analytical data. TLC (25% EtOAc/Hexane, $KMnO_4$): Rf 0.90; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.40 (ddd, J = 17.1, 10.2, 8.8 Hz, 1H), 5.05 (dd, J = 17.1, 1.8 Hz 1H), 4.85 (dd, J = 10.2, 1.8 Hz 1H), 1.40-1.24 (m, 12H), 1.12 (dddd, J = 8.6, 8.6, 4.3, 4.3 Hz, 1H), 0.91 (dd, J = 6.7, 6.7 Hz, 3H), 0.78-0.70 (m, 1H), 0.55 (ddd, J = 8.3, 4.3, 4.3 Hz, 1H), 0.55 (ddd, J = 8.2, 5.5, 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.3, 110.8, 33.8, 31.9, 29.4, 29.4, 29.3, 22.7, 22.5, 21.1, 14.1, 13.9; IR (neat): cm^{-1} 2925, 2854, 1636, 1026; HRMS (EI) calcd for $C_{12}H_{22}$: 160.1722; found: 160.1718. $[M^+]$; HPLC: Chiralcel OD, 2.5% *i*PrOH/hexane, 1.00mL/min., UV detection at 254 nm, major peak at 10.6 min., minor peak at 12.1 min., 95% ee.

4.5.32 1-((((1*S*,2*R*)-2-vinylcyclopropyl)methoxy)methyl)benzene (26c)

At room temperature, to a flame-dried round bottom flask, was added **20** (0.2 mmol), 2,6-lutidine (0.2 mmol) and 2 mL of dichloromethane. The mixture was stirred for 1 min, and then $SOCl_2$ (0.2 mmol) was added slowly. The reaction mixture was stirred at room temperature for 4 h. After removing the solvent, the product was purified by flash chromatography. Flash chromatography (2.5% EtOAc/Hexane) yielded a colourless oil (56% yield), which gave satisfactory analytical data. TLC (25% EtOAc/Hexane, $KMnO_4$): Rf 0.80; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.26 (m, 5H), 5.42 (ddd, *J* = 17.1, 10.2, 8.6 Hz, 1H), 5.08 (dd, *J* = 17.1, 1.7 Hz 1H), 4.88 (dd, *J* = 10.3, 1.3 Hz 1H), 4.54 (d, *J* = 2.5 Hz, 2H), 3.43 (dd, *J* = 10.4, 6.5 Hz, 1H), 3.35 (dd, *J* = 10.5, 6.9 Hz, 1H), 1.37-1.30 (m, 1H), 1.20 (dddd, *J* = 13.8, 6.7, 6.7, 4.2 Hz, 1H), 0.68 (dd, *J* = 7.5, 1.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.7, 128.4, 128.3, 127.7, 127.5, 112.2, 73.2, 72.4, 20.8, 20.3, 11.9; IR (neat): cm^{-1} 2855, 1636, 1094, 1028; HRMS (EI) calcd for $C_{13}H_{16}O$: 188.1201; found: 188.1206. [M^+]; HPLC: Chiralcel OD, hexane, 1.00mL/min., UV detection at 220 nm, major peak at 12.4 min., minor peak at 8.0 min., 90% ee.

4.5.33 1-(2-((1*S*,2*S*,3*R*)-2-methyl-3-vinylcyclopropyl)ethyl)benzene (27)



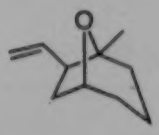
Flash chromatography (Hexane) gave the pure product as a colourless oil with dr 8:1 (78% yield). TLC (25% EtOAc/hexane, $KMnO_4$): Rf 0.90; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.16 (m, 5H), 5.55 (ddd, *J* = 17.1, 10.3, 9.1 Hz, 1H), 5.05 (dd, *J* = 17.1, 2.1 Hz 1H), 4.95 (dd, *J* = 10.3, 2.1 Hz 1H), 2.70 (ddd, *J* = 7.6, 7.6, 3 Hz, 1H), 1.60 (dddd, , *J* = 14.3, 14.3, 6.7, 6.7 Hz 2H), 1.22 (dddd, *J* = 8.7, 8.7, 4.5 Hz, 1H), 1.03 (d, , *J* = 6.3 Hz, 1H), 0.81-0.75 (m, 1H),

0.56 (dddd, J = 6.8, 6.8, 4.7, 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.4, 138.2, 128.5, 128.2, 125.6, 113.5, 35.8, 35.6, 27.7, 27.6, 20.3, 13.6; IR (neat): cm^{-1} 2926, 1632, 1453; HRMS (EI) calcd for $C_{14}H_{18}$: 186.1409; found: 186.1414. [M^+] HPLC: Chiralcel OD, 2.5% *i*PrOH/hexane, 1.00mL/min., UV detection at 254 nm, major peak at 20.2 min., minor peak at 23.7 min., 94% ee.

4.5.34 General procedure for the synthesis of compounds 25.

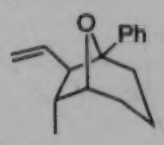
At -78 °C, to a flame-dried round bottom flask, was added **15** (0.2 mmol), ketoaldehyde (0.2 mmol) and 2 mL of dichloromethane. The mixture was stirred for 5 min, then BF_3-Et_2O (0.2 mmol) was added. The reaction mixture was stirred additional 12 h at -78 °C and 2 h at 0 °C, then quenched with an aqeous $NaHCO_3$ solution, extracted with ether, dried over anhydrous Na_2SO_4 and filtered. The products were purified by flash chromatography. The relative stereochemistry of **25a** was assigned based on TROESY NMR technique. Structure of **25b** assigned based on TROESY NMR technique, proved by X-ray diffraction.

4.5.35 1-methyl-7-vinyl-8-oxa-bicyclo[3.2.1]octane (25a)



Flash chromatography (5% EtOAc/hexanes) gave the pure product as a colourless oil (55% yield), which gave satisfactory analytical data. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.72 (ddd, J = 17.1, 9.8, 9.8 Hz, 1H), 4.94-4.86 (m, 2H), 4.36 (d, J = 7.6 Hz, 1H), 2.58 (ddd, J = 9.6, 9.6, 5.0 Hz 3H), 2.25 (dd, J = 12.8, 9.1 Hz, 1H), 1.82 (ddd, J = 12.4, 7.5, 5.0 Hz, 1H), 1.74-1.28 (m, 6H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.2, 113.5, 81.9, 75.3, 50.1, 38.7, 38.3, 30.4, 24.0, 17.2; IR (neat): cm^{-1} 2937, 1639, 1446, 1049; GC-Mass: [M^+]=162. $[\alpha]^{25}_D$ -3.57 (c = 0.3, $CHCl_3$). HPLC: Chiralcel OD, 7.5% *i*PrOH/Hexane, 0.50 mL/min., UV detection at 225 nm, major peak at 16.8 min., minor peak at 26.2 min., 97% ee.

4.5.36 6-methyl-1-phenyl-7-vinyl-8-oxa-bicyclo[3.2.1]octane (25b)



Flash chromatography (5% EtOAc/hexanes) gave the pure product as a colourless oil (77% yield), which gave satisfactory analytical data. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.16 (m, 5H), 5.10 (ddd, J = 16.9, 9.8, 9.8 Hz, 1H), 4.80 (dd, J = 16.9, 2.1 Hz, 2H), 4.66 (dd, J = 9.8, 2.1 Hz, 1H), 4.30 (bs, 1H), 2.50 (dd, J = 9.7, 7.2 Hz, 3H), 2.15 (dddd, J = 7.1, 7.1, 7.1, 7.1 Hz, 1H), 2.00-1.60 (m, 6H), 1.13 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): d 144.2, 141.6, 127.5, 126.1, 125.6, 112.8, 85.6, 78.1, 58.6, 46.0, 38.9, 25.3, 17.8, 11.7; IR (neat): cm^{-1} 2917, 1637, 1446, 1052; HRMS (EI) calcd for $C_{16}H_{20}O$: 228.1514; found: 228.1515. $[\alpha]^{25}_D$ +30.08 (c = 0.35, $CHCl_3$). HPLC: Chiralcel OD, Hexane, 1.00 mL/min., UV detection at 254 nm, major peak at 7.0 min., minor peak at 3.6 min., 98% ee.

4.6 References:

1. Roush, W. R.; Grover, P. T. *Tetrahedron Lett.* **1990**, *31*, 7567-7570.
2. (a) Roush, W. R.; Pinchuk, A. N.; Micalizio, G. C. *Tetrahedron Lett.* **2000**, *41*, 9413-9417. (b) Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **1997**, *62*, 1112-1124. (c) Heo, J.; Holson, E. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1697-1700. (d) Tinsley, J. M.; Mertz, E.; Chong, P. K.; Rarig, R. F.; Roush, W. R. *Org. Lett.* **2005**, *7*, 4245-4248.
3. (a) Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644-13645. (b) Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 1411-1414. (c) Hicks, J. D.; Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 5509-5512.
4. Barrett, A. G. M.; Braddock, D. C.; Koning, P. D.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 375-380.
5. Sarkar, T. K.; Haque, S. A.; Basak, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1417-1419. For related references, see: (a) Smitrovich, J. H.; Woerpel, K. A. *Synthesis* **2002**,

2778-2785. (b) Fleming, I.; Ghost, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2733-2738.

6. Matteson, D. S. *Acc. Chem. Res.* **1988**, *21*, 294-300.
7. Carosi, L.; Hall, D. G. *Angew. Chem., Int. Ed.* **2007**, *46*, in press.
8. (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11585-11587. (b) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518-4519. (c) Carosi, L.; Lachance, H.; Hall, D. G. *Tetrahedron Lett.* **2005**, *46*, 8981-8985.
9. Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123-130.
10. Hoffmann, R. W.; Neil, G.; Schlapbach, A. *Pure Appl. Chem.* **1990**, *62*, 1993.
11. (a) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160-10161. (b) Gravel, M.; Lachance, H.; Lu, X.; Hall, D. G. *Synthesis* **2004**, 1290-1302.
12. (a) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1997**, *95*, 1293-1316. (b) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063-2192.
13. (a) Mohr, P. *Tetrahedron Lett.* **1993**, *34*, 6251-6254. (b) Cassidy, J. H.; Marsden, S. P.; Stemp, G. *Synlett.* **1997**, 1411-1413. (c) Meyer, C.; Cossy, J. *Tetrahedron Lett.* **1997**, *38*, 7861-7864.
14. Reissig, H.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151-1196.
15. Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J.; Yuan, H. *J. Am. Chem. Soc.* **2001**, *123*, 2964-2969.
16. Pietruszka, J.; Schone, Niklas. *Eur. J. Org. Chem.* **2004**, 5011-5019.
17. Tsal, D. J. S.; Matteson, D. S. *Organometallics* **1983**, *2*, 236-241.
18. Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 1529-1535.

Appendix X-Ray Crystallography Report of Compound 25b (Chapter 4)

STRUCTURE REPORT

XCL Code: DGH0605 **Date:** 13 December 2006

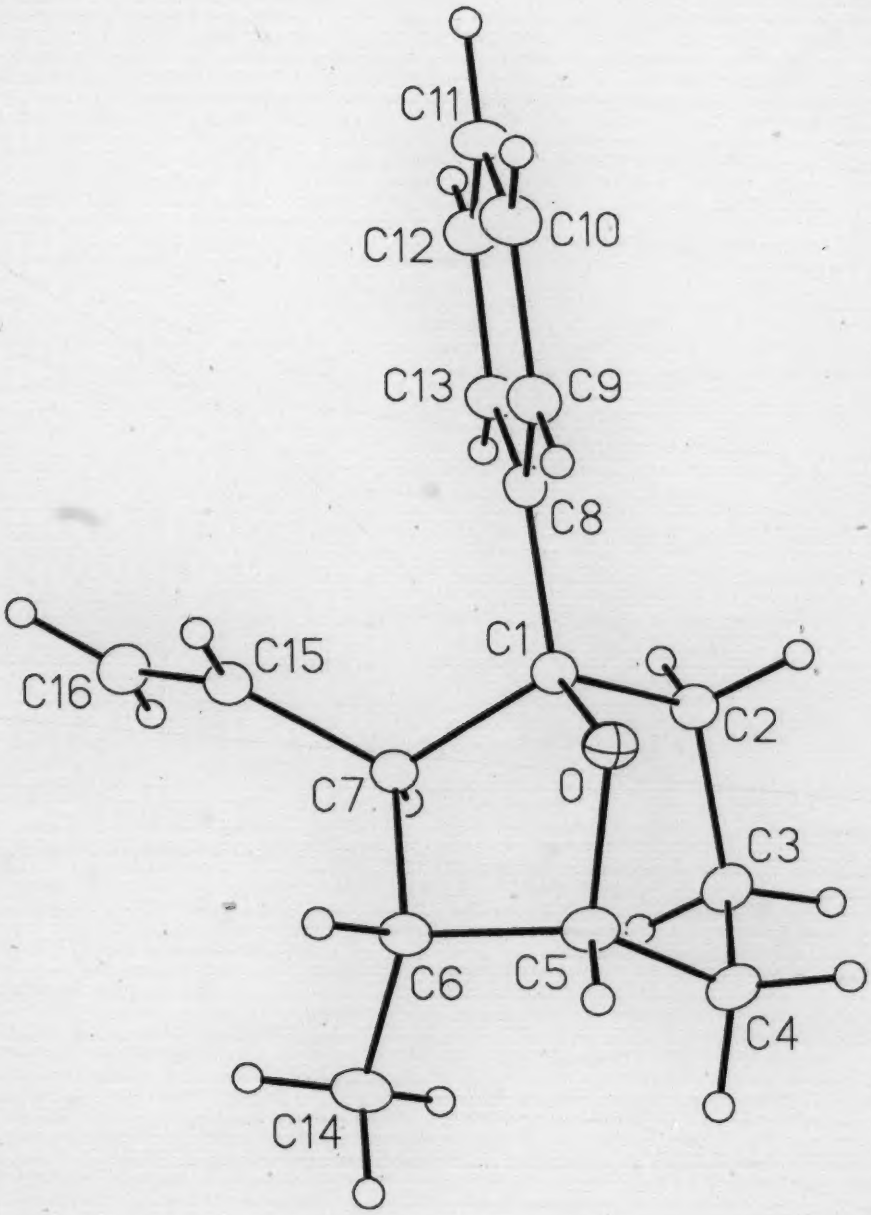
Compound: 6-Methyl-1-phenyl-7-vinyl-8-oxabicyclo[3.2.1]octane
Formula: $C_{16}H_{20}O$

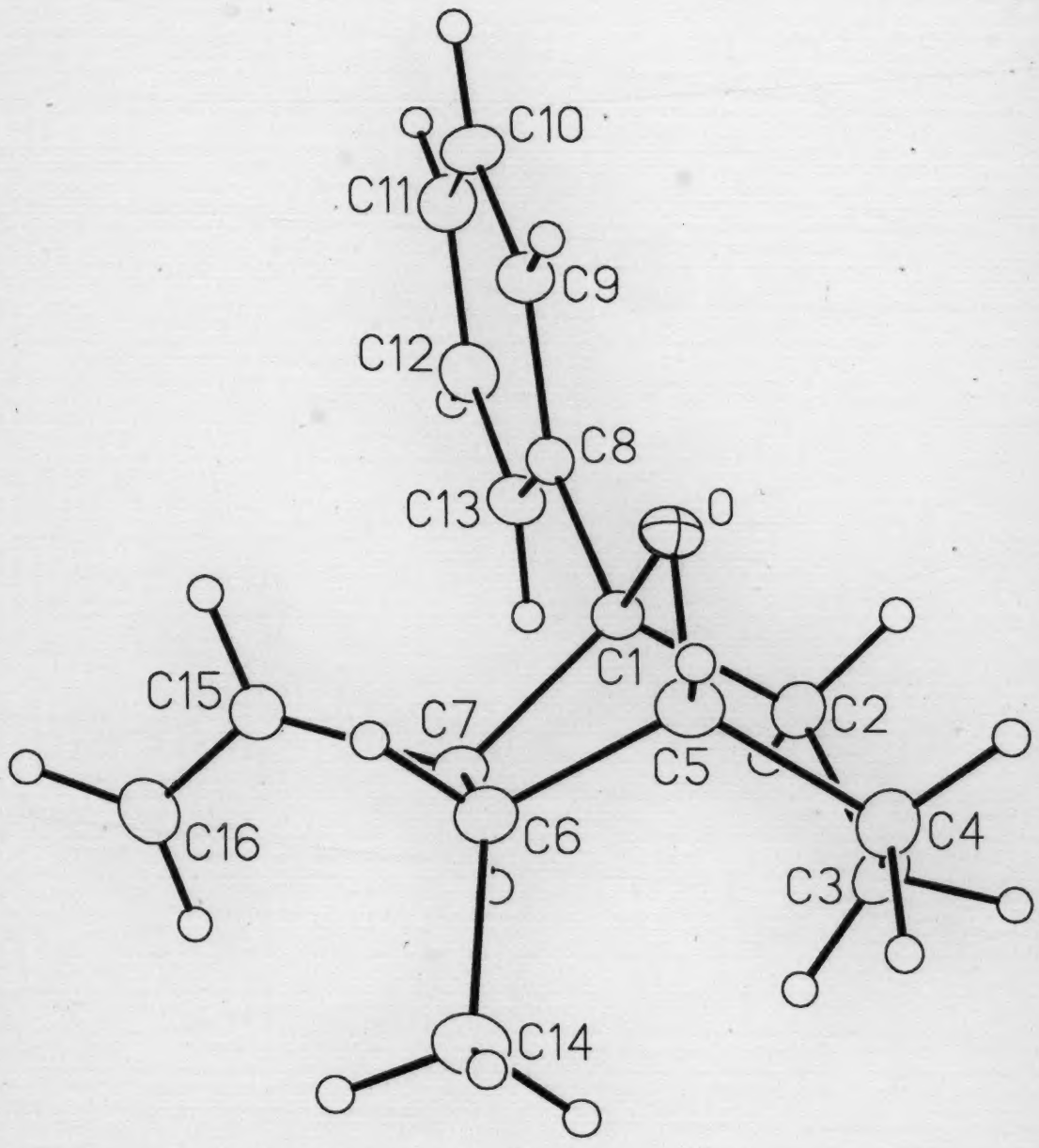
Supervisor: D. G. Hall **Crystallographer:** R. McDonald

Figure Legends

Figure 1. Perspective view of the 6-methyl-1-phenyl-7-vinyl-8-oxabicyclo[3.2.1]octane molecule showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters.

Figure 2. Alternate view of the molecule.


C11
C12
C10
C13
C9
C8
C1
C15
C16
C2
C7
O
C3
C6
C5
C4
C14


C10
C11
C9
C12
C8
C13
O
C1
C15
C7
C2
C5
C16
C6
C4
C3
C14

List of Tables

Table 1. Crystallographic Experimental Details

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Table 3. Selected Interatomic Distances

Table 4. Selected Interatomic Angles

Table 5. Torsional Angles

Table 6. Anisotropic Displacement Parameters

Table 7. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Table 1. Crystallographic Experimental Details

A. Crystal Data	
formula	$C_{16}H_{20}O$
formula weight	228.32
crystal dimensions (mm)	0.60 □ 0.30 □ 0.17
crystal system	orthorhombic
space group	$P2_12_12_1$ (No. 19)
unit cell parameters[a]	
a (Å)	7.7032 (5)
b (Å)	8.2335 (5)
c (Å)	20.6614 (13)
V (Å^3)	1310.43 (14)
Z	4
ρ_{calcd} (g cm^{-3})	1.157
μ (mm^{-1})	0.070
B. Data Collection and Refinement Conditions	
diffractometer	Bruker PLATFORM/SMART 1000 CCD[b]
radiation (□ [Å])	graphite-monochromated Mo K□ (0.71073)
temperature (°C)	–80
scan type	□ scans (0.3°) (15 s exposures)
data collection 2□ limit (deg)	52.72
total data collected	10486 ($-9 \le h \le 9$, $-10 \le k \le 10$, $-25 \le l \le 25$)
independent reflections	2678 (R_{int} = 0.0209)
number of observed reflections (*NO*)	2469 [$F_o^2 \ge 2\sigma(F_o^2)$]
structure solution method	direct methods (*SHELXS–86*[c])
refinement method	full-matrix least-squares on F^2 (*SHELXL–93*[d])
absorption correction method	multi-scan (*SADABS*)
range of transmission factors	0.9882–0.9593
data/restraints/parameters	2678 [$F_o^2 \ge -3\sigma(F_o^2)$] / 0 / 154
Flack absolute structure parameter[e]	–0.4 (13)
goodness-of-fit (S)[f]	1.084 [$F_o^2 \ge -3\sigma(F_o^2)$]
final R indices[g]	
R_1 [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0321
wR_2 [$F_o^2 \ge -3\sigma(F_o^2)$]	0.0812
largest difference peak and hole	0.161 and –0.161 e Å^{-3}

[a]Obtained from least-squares refinement of 7286 reflections with $5.32° < 2\theta < 52.58°$.

[b]Programs for diffractometer operation, data collection, data reduction and absorption correction were those supplied by Bruker.

[c]Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.

(continued)

Table 1. Crystallographic Experimental Details (continued)

[d]Sheldrick, G. M. *SHELXL-93*. Program for crystal structure determination. University of Göttingen, Germany, 1993.

[e]Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881; Flack, H. D.; Bernardinelli, G. *Acta Crystallogr.* **1999**, *A55*, 908–915; Flack, H. D.; Bernardinelli, G. *J. Appl. Cryst.* **2000**, *33*, 1143–1148. The Flack parameter will refine to a value near zero if the structure is in the correct configuration and will refine to a value near one for the inverted configuration. The low anomalous scattering power of the atoms in this structure (none heavier than oxygen) implies that the data cannot be used for absolute structure assignment, thus the Flack parameter is provided for informational purposes only.

[f]$S = [\Box w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\Box^2(F_o^2) + (0.0378P)^2 + 0.1696P]^{-1}$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$).

[g]$R_1 = \Box||F_o| - |F_c||/\Box|F_o|$; $wR_2 = [\Box w(F_o^2 - F_c^2)^2/\Box w(F_o^4)]^{1/2}$.

Table 2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O	0.14583(12)	0.15546(11)	0.29344(4)	0.0348(2)*
C1	0.17828(16)	0.19484(15)	0.36055(6)	0.0292(3)*
C2	0.00861(17)	0.26518(17)	0.38806(7)	0.0366(3)*
C3	-0.14064(18)	0.14289(18)	0.38323(7)	0.0431(3)*
C4	-0.14136(19)	0.05618(19)	0.31802(7)	0.0455(3)*
C5	0.04097(18)	0.01062(17)	0.29653(6)	0.0376(3)*
C6	0.14569(19)	-0.09646(16)	0.34290(6)	0.0358(3)*
C7	0.21980(16)	0.02642(15)	0.39249(6)	0.0307(3)*
C8	0.32327(16)	0.31851(15)	0.36355(6)	0.0302(3)*
C9	0.41365(18)	0.36656(17)	0.30848(7)	0.0376(3)*
C10	0.5424(2)	0.48432(18)	0.31235(8)	0.0481(4)*
C11	0.58197(19)	0.55528(18)	0.37073(8)	0.0492(4)*
C12	0.4949(2)	0.50734(18)	0.42581(8)	0.0467(4)*
C13	0.36794(19)	0.38922(16)	0.42249(7)	0.0384(3)*
C14	0.0511(2)	-0.24183(18)	0.37219(8)	0.0508(4)*
C15	0.40707(17)	-0.00552(16)	0.40675(7)	0.0372(3)*
C16	0.4670(2)	-0.05267(19)	0.46305(8)	0.0523(4)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table 3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
O	C1	1.4457(14)	C6	C14	1.5261(19)
O	C5	1.4418(15)	C7	C15	1.4957(18)
C1	C2	1.5384(18)	C8	C9	1.3914(18)
C1	C7	1.5686(17)	C8	C13	1.3929(18)
C1	C8	1.5127(17)	C9	C10	1.389(2)
C2	C3	1.5316(19)	C10	C11	1.374(2)
C3	C4	1.525(2)	C11	C12	1.378(2)
C4	C5	1.520(2)	C12	C13	1.3811(19)
C5	C6	1.5317(19)	C15	C16	1.310(2)
C6	C7	1.5489(17)			

Table 4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C1	O	C5	103.88(9)	C5	C6	C14	116.62(12)
O	C1	C2	106.97(10)	C7	C6	C14	115.21(11)
O	C1	C7	103.92(9)	C1	C7	C6	102.94(9)
O	C1	C8	108.54(9)	C1	C7	C15	115.78(10)
C2	C1	C7	110.52(10)	C6	C7	C15	111.77(11)
C2	C1	C8	111.02(10)	C1	C8	C9	121.82(11)
C7	C1	C8	115.29(10)	C1	C8	C13	119.97(11)
C1	C2	C3	111.48(11)	C9	C8	C13	118.20(12)
C2	C3	C4	111.60(12)	C8	C9	C10	120.57(13)
C3	C4	C5	111.73(11)	C9	C10	C11	120.36(13)
O	C5	C4	109.05(11)	C10	C11	C12	119.66(13)
O	C5	C6	102.05(10)	C11	C12	C13	120.35(14)
C4	C5	C6	116.48(12)	C8	C13	C12	120.84(13)
C5	C6	C7	103.41(10)	C7	C15	C16	124.52(14)

Table 5. Torsional Angles (deg)

Atom1	Atom2	Atom3	Atom4	Angle	Atom1	Atom2	Atom3	Atom4	Angle
C5	O	C1	C2	-74.32(11)	C2	C3	C4	C5	41.32(17)
C5	O	C1	C7	42.63(12)	C3	C4	C5	O	-57.55(16)
C5	O	C1	C8	165.82(10)	C3	C4	C5	C6	57.21(16)
C1	O	C5	C4	73.93(12)	O	C5	C6	C7	36.38(12)
C1	O	C5	C6	-49.86(12)	O	C5	C6	C14	163.92(11)
O	C1	C2	C3	59.88(14)	C4	C5	C6	C7	-82.26(13)
C7	C1	C2	C3	-52.62(14)	C4	C5	C6	C14	45.28(16)
C8	C1	C2	C3	178.14(11)	C5	C6	C7	C1	-10.77(12)
O	C1	C7	C6	-18.24(12)	C5	C6	C7	C15	-135.69(11)
O	C1	C7	C15	104.02(12)	C14	C6	C7	C1	-139.18(13)
C2	C1	C7	C6	96.20(11)	C14	C6	C7	C15	95.90(15)
C2	C1	C7	C15	-141.54(12)	C1	C7	C15	C16	128.39(14)
C8	C1	C7	C6	-136.89(11)	C6	C7	C15	C16	-114.17(16)
C8	C1	C7	C15	-14.63(16)	C1	C8	C9	C10	177.88(13)
O	C1	C8	C9	-5.62(16)	C13	C8	C9	C10	-1.3(2)
O	C1	C8	C13	173.51(11)	C1	C8	C13	C12	-177.25(12)
C2	C1	C8	C9	-122.92(13)	C9	C8	C13	C12	1.9(2)
C2	C1	C8	C13	56.21(15)	C8	C9	C10	C11	-0.1(2)
C7	C1	C8	C9	110.42(13)	C9	C10	C11	C12	1.0(2)
C7	C1	C8	C13	-70.44(15)	C10	C11	C12	C13	-0.3(2)
C1	C2	C3	C4	-42.84(16)	C11	C12	C13	C8	-1.1(2)

Table 6. Anisotropic Displacement Parameters (U_{ij}, Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O	0.0408(5)	0.0368(5)	0.0268(4)	0.0000(4)	-0.0021(4)	-0.0072(4)
C1	0.0303(6)	0.0305(6)	0.0267(6)	-0.0002(5)	0.0008(5)	-0.0018(5)
C2	0.0325(7)	0.0360(7)	0.0414(7)	-0.0033(6)	0.0016(6)	0.0004(6)
C3	0.0266(6)	0.0477(8)	0.0550(8)	-0.0016(7)	0.0032(6)	-0.0027(6)
C4	0.0358(7)	0.0470(8)	0.0538(9)	-0.0004(7)	-0.0108(7)	-0.0082(7)
C5	0.0421(8)	0.0384(7)	0.0322(6)	-0.0042(6)	-0.0040(6)	-0.0094(6)
C6	0.0361(7)	0.0318(7)	0.0393(7)	-0.0029(5)	0.0013(6)	-0.0058(6)
C7	0.0309(6)	0.0308(6)	0.0304(6)	0.0023(5)	0.0031(5)	-0.0036(5)
C8	0.0295(6)	0.0269(6)	0.0341(6)	0.0019(5)	0.0002(5)	0.0009(5)
C9	0.0389(7)	0.0355(7)	0.0385(7)	0.0018(6)	0.0045(6)	-0.0014(6)
C10	0.0432(8)	0.0437(8)	0.0574(9)	0.0095(7)	0.0123(7)	-0.0064(7)
C11	0.0369(7)	0.0372(7)	0.0736(11)	0.0042(7)	-0.0028(8)	-0.0121(6)
C12	0.0479(8)	0.0419(8)	0.0503(8)	-0.0030(7)	-0.0128(7)	-0.0087(7)
C13	0.0421(7)	0.0379(7)	0.0352(7)	0.0016(5)	-0.0018(6)	-0.0063(6)
C14	0.0547(9)	0.0369(8)	0.0607(10)	0.0030(7)	-0.0051(8)	-0.0153(7)
C15	0.0334(7)	0.0317(6)	0.0464(8)	0.0021(6)	-0.0015(5)	-0.0031(6)
C16	0.0459(9)	0.0472(9)	0.0637(10)	0.0094(8)	-0.0158(8)	-0.0039(8)

The form of the anisotropic displacement parameter is:

$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$

Table 7. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H2A	0.0264	0.2953	0.4340	0.044
H2B	-0.0224	0.3649	0.3639	0.044
H3A	-0.1293	0.0616	0.4183	0.052
H3B	-0.2524	0.2003	0.3892	0.052
H4A	-0.2129	-0.0433	0.3212	0.055
H4B	-0.1947	0.1278	0.2851	0.055
H5	0.0363	-0.0416	0.2529	0.045
H6	0.2464	-0.1403	0.3178	0.043
H7	0.1523	0.0170	0.4337	0.037
H9	0.3871	0.3184	0.2679	0.045
H10	0.6034	0.5160	0.2744	0.058
H11	0.6689	0.6369	0.3731	0.059
H12	0.5224	0.5558	0.4663	0.056
H13	0.3103	0.3558	0.4609	0.046
H14A	0.1303	-0.3012	0.4008	0.061
H14B	0.0115	-0.3139	0.3375	0.061
H14C	-0.0491	-0.2037	0.3971	0.061
H15	0.4882	0.0094	0.3726	0.045
H16A	0.3895	-0.0688	0.4983	0.063
H16B	0.5879	-0.0707	0.4687	0.063